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ORIGINAL ARTICLES

EFFECTS OF REPEATED POISONOUS SNAKEBITES IN MAN

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Poisonous snakebites are not rare in the United States, particularly in the southern and southwestern states. It has been estimated that from 2,000 to 3,000 snakebite accidents occur each year in the United States. During the 5-year period, 1950–54, there were 71 deaths from snakebites in the United States (Parrish[16]). This problem is not confined to the United States, for Swaroop and Grab[21] of the World Health Organization estimated that between 30,000 and 40,000 humans succumb to snakebites annually throughout the world.

There are 2 families of poisonous snakes indigenous to the United States: the Crotalidae, or pit vipers, and the Elapidae, or coral snakes. Of the pit vipers, the genera found in this country include the *Crotalus,* or rattlesnakes; the *Ancistrodon,* or moccasins (including the copperhead or highland moccasin and the cottonmouth or water moccasin); and the *Sistrurus,* or pigmy (massasauga) rattlesnakes. The pit vipers are responsible for most of the poisonous snakebites in this country; less than 2% of the bites are inflicted by coral snakes. One or more species of poisonous snakes has been reported as native to each state in this country.

The purpose of this study is to report the case histories of 14 patients who have experienced 2 or more envenomations by North American pit vipers. Repeated poisonous snakebites in the same individual are not as rare as some people think. This is particularly true among persons who handle poisonous snakes routinely. Poisonous snakebites are an occupational hazard among professional and amateur herpetologists, biologists, museum reptile curators, and religious faddists who use poisonous snakes as a part of their ceremonial regalia. Watt, Parrish and Pollard[22] described the case history of a professional herpetologist who survived the bites of 10 poisonous snakes which occurred over a 12-year period. Haast and Winer[10] reported the recovery of a

serpentarium director who had received repeated bites by various species of poisonous snakes, including the blue krait (*Bungarus caeruleus*). Githens[9] found that 163, or more than one in every 15, of the 2,342 snakebites in the United States he studied occurred among persons handling poisonous snakes. Allen and Neill[1] reported that 91 of the 600 snakebite cases they collected from newspaper accounts with follow-up questionnaires happened to amateur or professional snake handlers.

What are the effects of repeated poisonous snakebites in the same individual? The 3 concepts commonly held are: (1) that repeated envenomations will render the victim immune to venom and lessen the danger of future bites; (2) that the individual will develop an allergy to the complex proteins of the venoms, making each subsequent bite more dangerous and inviting the possibility of an anaphylactic reaction; and (3) that previous poisonous snakebites will have no effect on subsequent bites. A study of the effects of repeated poisonous snakebites in humans seemed worthwhile because there have been few case histories describing this phenomenon (Haast and Winer[10], Watt, Parrish and Pollard[22]), there have been no reports of successful immunization to the venoms of North American pit vipers among humans, and allergy to the venoms of North American pit vipers has not received much attention (Lownsberry[13], Parrish[17,18], Zozaya and Stadelman[25]).

Materials and Methods. The patients whose case histories are analyzed in this study are all professional herpetologists, snake handlers, wild animal dealers or biologists who live in Florida. All of the patients were adult males ranging from 22 to 45 years of age. At the time of interview, all of the patients were apparently in good health and working. Two of the patients are members of university faculties and the others are associated with commercial snake exhibits which cater primarily to tourists. Most of the poisonous snakebites among these individuals were incurred while catching, handling or "milking" the venom from snakes. For each snakebite accident the size and species of the offending reptile was known, owing to the victims' intimate knowledge of snakes.

Each patient was interviewed by us and the following data related to their envenomations were recorded: the name, age, sex and race of the victim; the size and species of the poisonous snake inflicting each bite; the anatomical location of each bite; the day, month and year each bite happened; a detailed account of the signs and symptoms which resulted from the bites; a list of therapeutic agents, including antivenin, used for treating the bites; and the presence of any anatomical defects or chronic conditions attributed to the snakebites. Hospital records were used to verify these reports in most instances. Only poisonous snakebites which resulted in clinical signs of envenomation were used in this study. Several of the patients had experienced scratches from snakes fangs or superficial poisonous snakebites, or both, which did not result in venom poisoning. These accidents were not classified as envenomations and were not included in the present study. It is possible for a poisonous snake to inflict a wound without injecting venom into it. The anatomical sites of the bites were examined for evidence of treatment (scars resulting from incisions or excisions) and sequelae.

In addition to a detailed history of the bites, a sample of blood was drawn from each patient for bilirubin determinations, Prausnitz-Küstner tests, and venom neutralization tests. Thirteen of the 14 patients were scratch tested for allergy to cottonmouth moccasin (*A. piscivorus*) and eastern diamondback rattlesnake (*C. adamanteus*) venoms. These venoms were selected for scratch testing because they were thought to be representative of North American pit viper venoms. Fresh, undiluted venoms, instead of dilute solutions of crystalline venoms, were used. The venom was applied with a toothpick to superficial 4 to 6 mm. long scratches on the forearm. The scratch tests were read 20 minutes later. A modified Prausnitz-Küstner test of local passive transfer of hypersensitivity was done with the serum of each patient having a positive scratch test. The technique used was that described by Kolmer, Spaulding and Robinson[12]. A detailed discussion of these techniques has been published previously (Parrish[17], Parrish, Watt and Arnold[18]).

Factors which influence the severity of a poisonous snakebite include: the size and species of the snake; the age, weight and general condition of the patient; the location and nature of the bite (a glancing scratch as opposed to deep impregnation of the venom); the amount of venom injected by the snake; and the toxicity of the venom of the specific snake. Since the exact amount of venom injected by the snake could not be determined, we used Wood, Hoback and Green's[24] clinical classification of the severity of pit viper venenations. They classified bites as: *Grade 1. Minimal Venenation.* "These include cases having a history of suspected snake bite plus localized signs including the presence of one or more puncture wounds, moderate pain or throbbing localized at the fang wounds, and an area of edema extending not more than a few inches from the point of initial venenation. The hospital course in the subsequent 12 hours provides no evidence of systemic involvement." *Grade 2. Moderate Venenation.* Patients classed in this group demonstrated the signs of Grade 1 poisoning during a brief early stage in their intoxication, but soon had more severe and widely distributed pain, and more marked edema which would continue to progress up an extremity toward the trunk during the first 12 hours of hospitalization. In most cases the edematous area involved about half the distance between the bite site and the trunk. Nausea, vomiting, and giddiness were usually present. Petechiae and ecchymoses were restricted to the area of edema. A low grade temperature usually developed and persisted for from one to four days." *Grade 3. Severe Venenation.* "These patients may resemble Grade 1 or Grade 2 on admission, but the course of their intoxication is rapidly progressive. These patients may arrive in shock within a few minutes of the time of injury. Within 12 hours the edematous area extends from a bite site on an extremity to or involving part of the trunk. Petechiae and ecchymoses are frequently generalized in distribution. During the first 12 hours of therapy the pulse becomes rapid and thready, the temperature becomes subnormal, and the patient approaches a state of shock." In addition, we have observed that coma and muscular twitching, either localized to the involved area or generalized, are common in Grade 3 venenation. Since these Grades of venenation indicate the severity of pit viper venom poisoning, changes in the Grades of venenation might indicate if subsequent bites become progressively worse or progressively less severe.

Results. Of the 14 patients with repeated poisonous snakebites, one patient experienced 12 different poisonous snakebites, one patient had 10 poisonous snakebites, 2 had 6 bites, one had 5 bites, 3 had 4 bites, one had 3 bites, and 5 had 2 bites. Thus, these 14 individuals had a total of 64 poisonous snakebites. Rather than describe in detail each of the snakebites suffered by these individuals, a summary of the case histories is presented in Table 1. This table lists the sequence of the snakebites, the severity of each envenomation, and the kind of snake inflicting each bite.

The anatomical sites of these bites were as follows: 36 on the fingers or thumb; 10 on the forearm; 8 on the hand; 7 on the leg; and 3 on the foot. Therefore, all of these snakebites were located on the extremities, 54 (84%) on the upper extremities and 10 (16%) on the lower extremities. The high proportion of bites on the upper extremities reflects the activities of the victims at the time of the bites. Most of these bites happened while the victims were handling snakes. Five patients had permanent local defects as a result of snakebites. One patient had his thumb amputated, and 3 others have atrophy, limitation of motion and a permanent deformity of a digit. These defects result from necrosis, gangrene and infection following envenomation. Another patient had atrophy of his shoulder muscles resulting from a poisonous snakebite on the forearm of the involved side. The muscle atrophy in this patient probably resulted from a neuritis associated with serum sickness following antivenin (horse serum) therapy. Aside from these defects and a few minor scars resulting from incisions and excisions used for mechanical removal of the venom, no other permanent anatomical defects were observed. These defects were thought to

TABLE 1.—REPEATED POISONOUS SNAKEBITES IN THE SAME INDIVIDUALS BY SEQUENCE OF BITES, KINDS OF SNAKES INVOLVED AND GRADES OF VENENATION

Patient	*Sequence of Snakebites*												*Total No. Bites*
	I	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*	*XI*	*XII*	
1. (WTN)	2 M	1 R	3 C	2 M	1 R	1 M	3 R	2 O	1 M	2 M	1 PR	1 M	12
2. (RA)	3 R	2 C	2 R	3 R	1 M	1 R	1 O	1 R	1 M	3 R			10
3. (BB)	1 R	2 C	3 R	3 O	1 PR	3 M							6
4. (HGW)	1 M	1 C	1 C	3 R	1 M	3 M							6
5. (RS)	2 R	3 R	1 PR	2 R	3 M								5
6. (WR)	2 M	1 C	1 C	3 M									4
7. (WP)	2 R	2 R	1 R	3 R									4
8. (JH)	1 R	2 M	3 R	2 R									4
9. (RT)	3 C	2 R	1 R										3
10. (JR)	2 M	1 C											2
11. (CT)	1 PR	1 R											2
12. (WA)	1 C	2 M											2
13. (CMB)	2 R	2 R											2
14. (AC)	1 R	2 R											2

R = Rattlesnake
PR = Pigmy Rattlesnake
C = Copperhead Moccasin
M = Cottonmouth Moccasin
O = Other Poisonous Snakes (foreign)

1 = Minimum Venenation
2 = Moderate Venenation
3 = Severe Venenation

result from the individual episodes of envenomation and not from the cumulative effects of repeated envenomations. As previously mentioned, all of these patients were apparently healthy and active. None of them gave a history of chronic liver or kidney disease. The serum bilirubin values obtained from these patients were all within normal limits. Hospital records showed that 8 of these patients had normal urinalyses following their most recent snakebite. The status of the urine of the other 6 patients was not known. The apparent lack of permanent hepatic and renal damage in these patients is somewhat surprising in view of the necropsy findings in humans who died from snake venom poisoning (Amorim and Mello[2], Jaffe[11]) and those in horses used for antivenin production (Githens[8]).

The kinds of snakes involved in these 64 snakebite accidents were: rattlesnakes (*Crotalus sp.*) inflicted 29 bites; cotton-mouth moccasins (*Ancistrodon piscivorus*) inflicted 18 bites; copperhead moccasins (*Ancistrodon contortrix*) inflicted 10 bites; pigmy rattlesnakes (*Sistrurus sp.*) caused 4 bites; and snakes which are not native to the United States (*Bothrops atrox, Coniophanes sp.,* and *Demansia olivacea*) caused 3 bites. Of the 29 rattlesnakes of the genus *Crotalus* which inflicted bites, the following species were involved: *C. adamanteus*, 17; *C. atrox*, 5; *C. horridus horridus*, 3; *C. horridus atricaudatus*, 2; *C. viridis viridis*, 4; and *C. viridis oreganus*, 1. Thus 61 out of the 64 snakes which bit these individuals were North American pit vipers. Table 2 shows the severity (Grades) of venenation resulting from bites by the various kinds of snakes. Thirty-one per cent of the bites inflicted by rattlesnakes (*Crotalus sp.*) resulted in Grade 3 severe venenation; whereas only 22% of cottonmouth moccasin bites and 20% of copperhead moccasin bites resulted in Grade 3 venenation. None of the pigmy rattlesnake (*Sistrurus sp.*) bites produced Grade 3 venenation. That the rattlesnakes (*Crotalus sp.*) produced the highest proportion of severe venenations was to be expected, since they generally are regarded as the most dangerous snakes in the United States.

TABLE 2.—CLASSIFICATION OF POISONOUS SNAKEBITES BY KIND OF SNAKE AND GRADE OF ENVENOMATION

	Severity (Grade) of Envenomation°			
Kind of Snake	*I*	*II*	*III*	*Total*
Rattlesnake	10	10	9	29
Pigmy Rattler	4	—	—	4
Copperhead Moccasin	6	2	2	10
Cottonmouth Moccasin	7	7	4	18
Other	1	1	1	3
Total	28	20	16	64

°I = Minimum Venenation
II = Moderate Venenation
III = Severe Venenation

Parrish[16] found that Crotalus species caused at least 77% of the fatalities from snakebites in this country, 90% of those for which the species was identified. Eastern diamondback (*C. adamanteus*) and western diamondback (*C. atrox*) rattlesnakes are especially dangerous, for by virtue of their enormous size, six to 8 feet in length, they produce large amounts of venom. The bites of pigmy rattlesnakes and copperhead moccasins are less dangerous. All of the pigmy rattlesnake bites and 60% of the copperhead moccasin bites resulted in Grade 1 or minimal venenation.

There was no clinical evidence from the 14 case studies summarized in Table 1 that permanent immunity developed as a result of repeated envenomations by North American pit vipers. Six (case histories 2, 3, 4, 5, 6, and 7)

of the 14 patients experienced Grade 3 or severe venenation from their last snakebite in spite of having been bitten 3 or more times previously by pit vipers. It might be argued that these patients didn't develop permanent immunity because they were bitten by different species of snakes. However, many of the patients in this study were bitten more than once by the same species and still failed to show clinical evidence of immunity. For example, the patient in case history 2 received 5 rattlesnake bites before his last bite by an eastern diamondback rattlesnake (*C. adamanteus*) which resulted in Grade 3, that is, severe venenation. Of his previous rattlesnake bites, 3 were by western diamondbacks (*C. atrox*) and 2 were by eastern diamondbacks (*C. adamanteus*). The patient described in case history 4 suffered 2 previous envenomations by cottonmouth moccasins (*A. piscivorus*) before his last bite by a cottonmouth moccasin which resulted in Grade 3 venenation. Likewise, the patients described in case histories 6 and 7 had received previous bites by snakes of the same species as the last one which bit them and produced Grade 3 venenation. In all, 8 patients (case histories 1, 2, 4, 6, 7, 8, 13, and 14) suffered either Grade 2 or Grade 3 venenation from species of snakes identical to the ones which had bitten them previously.

There was reason to expect the development of some cross immunity in these individuals from bites by various species of pit vipers. Minton[15] has demonstrated by the agar diffusion method that the venoms of North American rattlesnakes and moccasins possess common antigens. Criley[3] reported on a multivalent antivenin for snakes of the family Crotalidae which is produced by using only 4 venoms. Nevertheless, this antivenin affords protection against the venoms of many species of North and South American pit vipers (Gingrich and Hohenadel[7]). For example, this antivenin neutralizes the venoms of copperhead and cottonmouth moccasins, but these venoms are not used in the production of the antivenin. There was no clinical evidence that a protective level of permanent cross-immunity developed in these individuals with repeated envenomations.

The interval of time between bites may have been a factor which resulted in the lack of permanent immunity in some of these individuals. For example, the patient in case history 2 suffered 10 snakebites over a 12-year period: the shortest interval between bites was 6 months and the longest interval was 3 years. Patient 3 experienced 6 envenomations over a 17-year period; the shortest interval between bites was 8 months and the longest interval was 10 years. Patient 4 had 6 snakebites over a 23-year period; the shortest interval between bites was 5 months and the longest interval was 13 years. Other patients had snakebites which occurred closer together. For example, patient 5 was bitten by an eastern diamondback rattlesnake which caused Grade 2 venenation, and 5 months later he was bitten by another eastern diamondback which produced Grade 3 venenation. Patient 6 was bitten by copperhead moccasins 7 months apart and suffered Grade 1 venenation both times; patient 7 was bitten by eastern diamondback rattlesnakes 7 months apart and suffered Grade 2 venenation with the first bite and Grade 1 venenation with the second bite; patient 13 was bitten by eastern diamondback rattlesnakes 3 months apart and had Grade 2 venenation both times; and patient 14 was bitten by eastern diamondbacks 13 months apart, suffering Grade 1 venenation the first time and Grade 2 venenation the second time. Although many factors are involved in the severity of envenoma-

tion, these illustrations of bites by snakes of the same species within a relatively short period of time would seem to suggest that little, if any, permanent immunity develops from repeated "natural" envenomations.

Additional evidence of the lack of permanent immunity to North America pit viper venoms in these patients was obtained by means of venom neutralization tests in mice. *Crotalus adamanteus* venom was used in these tests. When the serum of the snakebite victims was compared with the serum of normal control subjects for venom neutralization potency, no significant differences were found (Criley[4]).

transfer of hypersensitivity. The areas on the forearms of the control subjects which were injected with 0.1 ml. of serum from the allergic patients and scratch tests 24 hours later exhibited large wheals with pseudopods and extensive surrounding erythema. These reactions were entirely different from the controls' original responses and, in fact, were almost identical to the reactions of the allergic patients. These findings would seem to establish the presence of pit viper venom allergy in these patients. Fortunately, none of these patients had experienced anaphylactic shock resulting from snake venom allergy.

TABLE 3.—PATIENTS' RESPONSES TO SCRATCH TESTS WITH PIT VIPER VENOMS

Patients	*M>R*	*R>M*	*R↑ = M↑*	*R↓ = M↓*	*Allergy M or R*	*Total*
Control subjects	7	1	6	6	–	20
Patients with repeated snakebites	5	–	1	3	4	13
Total	12	1	7	9	4	33

M = Cottonmouth moccasin (*A. piscivorus*) venom.
R = Eastern diamondback rattlesnake (*C. adamanteus*) venom.

Thirteen of the 14 patients with repeated poisonous snakebites were scratch tested for allergy to cottonmouth moccasin (*A. piscivorus*) and rattlesnake (*C. adamanteus*) venoms. Of these, 4 exhibited hypersensitivity to venom. Twenty normal patients, with no history of snakebites, were scratch tested to serve as a control group. See Table 3 for the results of the scratch tests. In general the allergic patients demonstrated *large wheals with pseudopods* and an extensive area of surrounding erythema; whereas the control subjects had smaller wheals with no pseudopods and less extensive surrounding erythema. The presence of allergy to venom in these 4 patients was confirmed by using a modified Prausnitz-Kustner test of local passive

Discussion. It seems apparent from these 14 case histories that no permanent immunity develops as a result of repeated envenomations by North American pit vipers. Permanent immunity to pit viper venoms has never been demonstrated in humans although, theoretically, it would seem possible. One factor which may have inhibited the development of permanent, active immunity in some of these patients was the administration of antivenin for treating the bites. When active and passive immunity are administered simultaneously, a high titer of passively transferred antibodies may inhibit the development of active (permanent) immunity (Downie *et al.*[5], Phair and Root[19]). However, 5 of the patients in this study (case histories 1, 6, 9, 11

and 12) have never received antivenin for the treatment of their snakebites. One or more envenomations in 12 of these patients were not treated with antivenin. Therefore, antivenin inhibition of active immunity would not seem a major factor in the lack of permanent immunity in these patients. Bites by different species of pit vipers may have accounted for some of the lack of permanent immunity. Inconsistencies in the dose of venom received at each bite may have played a role in the lack of permanent immunity. Permanent immunity in experimental animals is produced by increasing the dose of venom at frequent intervals of time. However, one of the most important reasons why these patients failed to develop a protective level of active immunity was the prolonged and irregular intervals between envenomations. It has been shown in horses used for antivenin production that when the injections of venom are stopped, the protective titer of antibodies rapidly wanes. Likewise, Essex and Markowitz[6] were able to produce temporary immunity to snake venom in dogs, but found this immunity declined about 90 days after the venom injections were stopped. Another very important factor is the short "incubation period" between a poisonous snakebite and the time when signs and symptoms of clinical envenomation become apparent. In contrast to infectious diseases which have an incubation period of from 14 to 21 days, the "incubation period" for snake venom poisoning is only 2 to 15 minutes. This very short latent period does not provide sufficient time for a "booster effect" on antibody production. A high titer of antibodies must be present at the time of the envenomation, or shortly thereafter, in order to neutralize the venom. Thus, while active immunization of humans to snake venoms probably is possible by frequent injections of venom, antivenin therapy would seem a much more rational approach to the problem.

This study would seem to indicate that blood from patients with a history of previous pit viper envenomations is no better for transfusions in treating snakebites than the blood of normal healthy persons who have not been snakebitten. We know of several instances where snakebite victims have been transported long distances to receive transfusions from persons who previously have been bitten. This practice is to be condemned. Regardless of their motivations, professional snake handlers, herpetologists, and physicians should discourage this practice.

Hypersensitivity to pit viper venoms is by no means rare among patients with repeated envenomations. Four of the patients in this study were allergic to cottonmouth moccasin or rattlesnake venoms, or both. Snake venoms are complex substances comprised chiefly of proteins (Porges[20]). Thus, there is a definite possibility of developing allergy to these animal proteins. Deaths have been reported which resulted from allergy to other animal venoms including bee, wasp and yellowjacket venoms (Marshall[14]). It seems entirely possible that occasional deaths from snakebites, in individuals who have been previously bitten, may result from snake venom allergy. Some individuals with snake venom allergy may exhibit hypersensitivity to the venom of a zoologically related species of snakes. For example, the patient described in case history 1 is allergic to eastern diamondback rattlesnake (*C. adamanteus*) venom, but received his bites from other rattlesnake species (*S. miliarius miliarius* and *C. horridus atricaudatus*). The patients described in case histories 6 and 10 were found allergic to rattlesnake venom (*C. adamanteus*) although they were bit-

ten by copperhead (*A. contortrix*) and cottonmouth (*A. piscivorus*) moccasins. Weiss[23] found that mice rendered hypersensitive to South American snake venoms may also exhibit hypersensitivity to the venom of a closely related species. These findings are consistent with the observations of Minton[15] who showed that the venoms of pit vipers have common antigens. It is interesting that only one (case history 1) of the 4 patients with venom allergy had symptoms of allergy while working with poisonous snakes or their venoms. This case history has been discussed in detail elsewhere (Parrish, Watt and Arnold[18]).

Serious poisonous snakebites need not terminate fatally. All of the patients in this study are experts in first-aid measures used for snakebite. Prompt application of a tourniquet with incision and suction of the wound undoubtedly saved some of their lives. Also antivenin was used rather freely (40 to 50 ml.) in most of the episodes of Grade 2 and Grade 3 venenation. Antivenin may be considered specific therapy for pit viper envenomation. As a result of Antivenin (made from horse serum) treatment, 4 of the patients developed hypersensitivity to horse serum. In some instances the danger of Antivenin (horse serum) allergy is more threatening than venom intoxication to patients who have been snakebitten.

The results obtained in this study would seem to indicate that repeated envenomations by North American pit vipers do not produce permanent immunity in man, that some persons with repeated poisonous snakebites develop allergy to snake venoms which may make subsequent bites more dangerous, and that the severity of subsequent bites in nonallergic patients depends on the characteristics of the particular snakebite rather than the cumulative effects of previous snakebites.

Summary. 1. The effects of repeated poisonous snakebites in 14 patients were studied. One patient had 12 different poisonous snakebites, one patient had 10 snakebites, 2 had 6 bites, one had 5 bites, 3 had 4 bites, one had 3 bites, and 5 had 2 bites. All but 3 of the snakes inflicting these bites were North American pit vipers.

2. Five patients had permanent local defects such as atrophy of muscles and amputations of digits following snakebites. There was no evidence of chronic liver or kidney disease in these patients.

3. There was no clinical or laboratory evidence that these patients developed permanent immunity to pit viper venoms. The lack of permanent immunity was attributed primarily to the prolonged and irregular intervals between envenomations and the short latent period between a bite and the development of clinical envenomation which does not allow sufficient time for a "booster effect" on antibody production. Other possible contributing factors were bites by different species of snakes, antivenin inhibition of active immunity, and inconsistencies in the doses of venom injected.

4. Thirteen of the 14 patients with repeated envenomations were scratch tested for snake venom allergy. Of these, 4 were found allergic to rattlesnake or moccasin venoms, or both. Some patients exhibited allergy to the venom of snakes zoologically related to the species which bit them. For example, a patient may become allergic to moccasin venom even though he was bitten previously by rattlesnakes. The severity of repeated snakebites in nonallergic patients depends on the characteristics of the individual envenomation and not on the cumulative effects of previous snakebites.

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(Interlingua on page 318)

SUMMARIO IN INTERLINGUA

(See page 304 for original article)

Minus Communmente Recognoscite Actiones De Atropina Super Le Rhythmo Cardiac

1. Sulfato de atropina es un potente blocante parasympatholytic.

2. Le action de atropina super le corde passa per tres distincte phases. Illos es un effecto vagotonic initial, un periodo transiente de imbalancia vagal a differente nivellos del systema de conduction, e un periodo prolongate final de blocage parasympathic.

3. Le alterationes observate durante le phase initial del action de atropina es simile al alterationes vidite quando imbalancia vagal es producite per varie simple medios respiratori.

4. Iste phase initial del action de atropina pote esser utilisate in le investigation de certe arrhythmias e defectos de conduction.

5. Ben que le actiones cardiac de atropina in le usual doses clinic es benigne, quando illos es combinate con le action de drogas como neostigmina, serie arrhythmias e defectos de conduction pote supervenir.

ABSORPTION AND UTILITY OF LOBELINE AS A SMOKING DETERRENT*

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Lobeline salts have been used successfully for years to aid persons desiring to cut down or stop smoking tobacco (Dorsey[1], Rapp and Olen[2], Wright and Littauer[3]). Previous reports have indicated that a buffered preparation of lobeline is desirable for this purpose because it produces its objective in very small quantities (2 mg.), and there are virtually no undesirable side effects upon gastrointestinal and cardiovascular reactions (Rapp and Olen[2]).

This paper seeks to extend knowledge about lobeline as an aid to chronic smokers who should, or want to, curb their smoking activities.

Data were obtained in two new areas: a) the absorption of lobeline and its consequent blood level, and b) the relationship between lobeline blood level and its effectiveness in curbing smoking of cigarettes.

As an extension of previous knowledge, we repeated the study which showed the effectiveness of buffered lobeline as a smoking deterrent, and the failure of nonbuffered lobeline to act in this manner.

Procedures and Results. A. LOBELINE LEVEL DETERMINATIONS. For determining the blood level changes of lobeline, the following procedures were employed:

Twenty-five men and 25 women, habitual smokers ranging in age from 21 through 48 years, were used for the study. Ten milliliter blood samples were obtained by venipuncture at 8 a.m. for a period of 6 days. This preliminary "dry run" was deemed necessary to ascertain whether any substance usually included in the daily diet of these subjects might possibly produce errors in the analytic procedure.

Prior to this investigation there was no published simple and suitable method for determining micro-quantities of lobeline in blood. A great deal of effort, therefore, was spent in attempting to devise such a suitable method. It is pleasing to report that a workable method has been devised. Since this method is new, it has been submitted for publication in a suitable analytical journal, where all of the ramifications of the procedure will be presented. It seems sufficient at this point to state that the method consists essentially of a colorimetric assay of the alkaloid, lobeline. The method seems to be specific, in that several other alkaloids, for example nicotine, caffeine, morphine and stramonium have all

*A part of the expenses of this study was defrayed by a grant from the Campana Company, Batavia, Illinois.

yielded negative results under the conditions of the test.

In outline, the method consists of treating suitable prepared, deproteinized blood filtrates with salicyloyl hydrazide. This treatment is followed by coupling with diazotized sulfanilic acid. The resulting color can be measured by suitable colorimeters. Within specified working limits, the color follows the Beer-Lambert Law, and therefore may be employed for quantitative estimation of the alkaloid. The useful range and reproducability of the method have been ascertained. Recovery of known lobeline concentrations in plasma fall between 90 and 103%, in the range from 0.2 to 2.0 μg. per ml.

Each subject was given a supply of capsules in one of the following categories: 1) Corn Starch (as placebo control); 2) 2 mg. lobeline sulfate suspended in corn starch; 3) the Bantron preparation,† powdered and capsulated.

The subjects were given the capsules with the instructions that one was to be taken three times a day, after meals. All subjects had been under observation with regard to their smoking habits for a suitable pre-experimental period. Their smoking habits were followed daily according to the procedure previously reported (Rapp and Olen[2]).

Daily blood samples were obtained and analyzed. After 6 days on the test, 2 weeks intervened while no medication was given, but the first week daily blood samples were taken. The second week was a period of rest and recuperation.

Then commenced another similar 3-week test period, identical with the above, but with the single exception that another group of capsules was substituted for those employed during the first period.

After three such experimental periods of 3 weeks each, every subject on the test had been evaluated for his response towards each of the prescribed medications.

The test was run on the "double blind" technique. At no time during the test did the subject or the dispensing technician know the identity of the material in the respective capsules.

Results. After the experimental periods, the results from each subject were collected and analyzed. A resume of these results is found in Figs. 1, 2 and 3.

Figure 1 presents the blood levels of lobeline obtained in the three experimental periods. The graph shows the average values of all 50 subjects. It can be seen that only the buffered formulation produced an appreciable blood lobeline level when analyzed as indicated above.

Fig. 2 relates the number of smokes per day per subject with the lobeline blood level. It will be seen that a level of from 100 to 120 μg. per 100 ml. blood produced the maximum effect, with the minimum number of smokes consumed per day. Only the buffered formulation produces such blood level, as indicated in Fig. 1.

Figure 3 presents the data obtained in another form. This figure shows the number of subjects *not smoking*, related to the blood lobeline level. The figure illustrates that the maximum number not smoking was reached when the blood level values approached 140 μg. lobeline per 100 ml. blood. It must be pointed out again that the unbuffered lobeline did not produce such blood levels, while the buffered formulation did so consistently.

B. UTILITY AS SMOKING DETERRENT. The following study was conducted to attempt to explain apparently nega-

†The Bantron formulation consists of 2 mg. lobeline sulfate suspended in a carrier of tricalcium phosphate and magnesium carbonate, slow-acting and fast-acting ant-acid compounds, respectively.

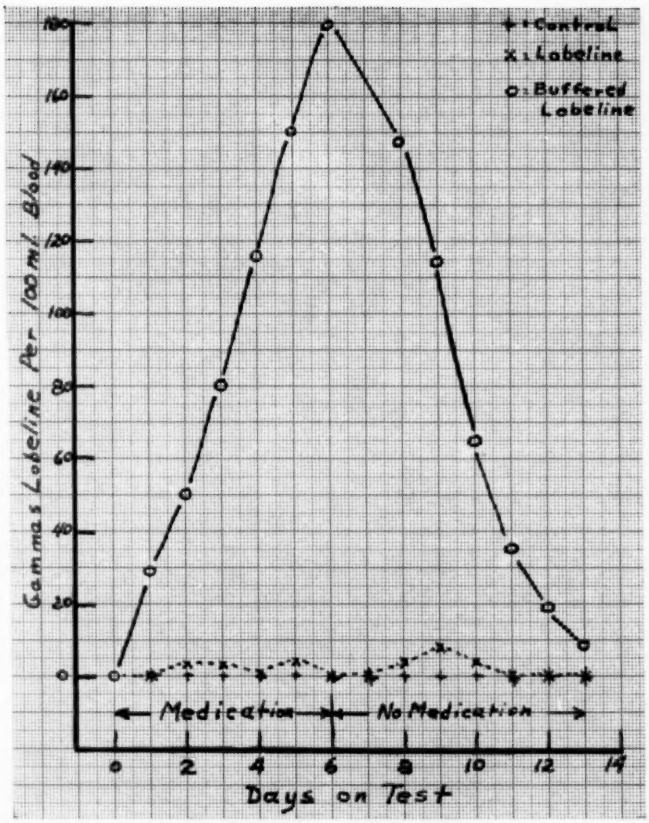

Fig. 1.—Blood levels of lobeline.

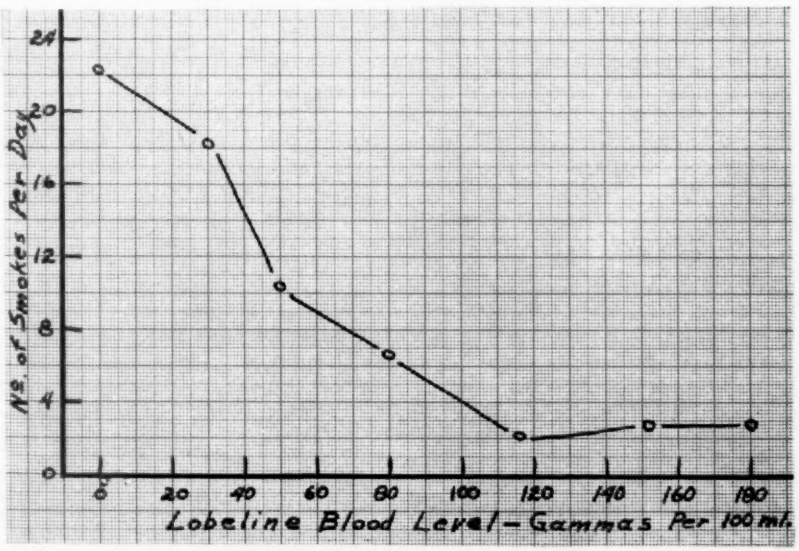

Fig. 2.—Relation between blood level and cigarettes smoked.

tive results in curbing the tobacco habit with subjects who professed no desire to stop smoking, as well as with a minority of subjects (approximately 20% based on previous studies) who did want to stop, or at least cut down.

Two groups of subjects were investigated:

A. Twenty-five subjects *not desiring to stop smoking,*

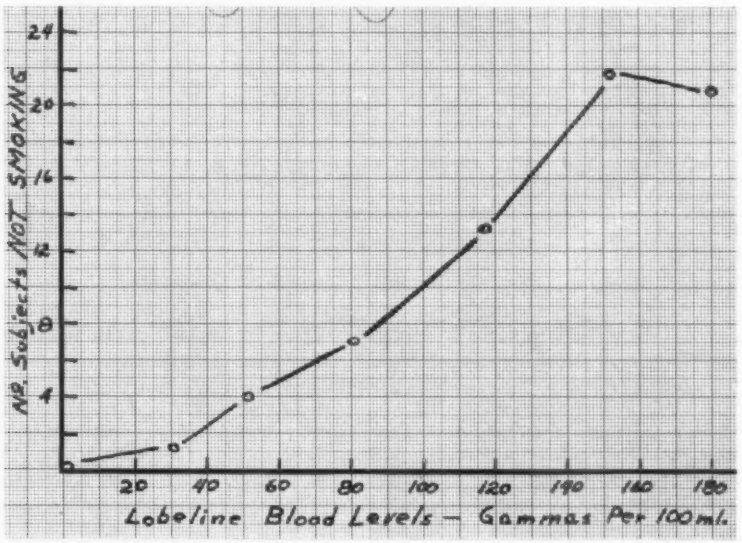

Fig. 3.—Relation between blood levels and number of subjects not smoking.

B. Twenty-eight subjects who wanted to stop smoking, or at least to cut down the amount smoked.

The subjects were chosen for each group so as to make these groups as homogeneous as possible with respect to the number of cigarettes smoked per day.

The subjects of both groups were told only that the substances being investigated might help them to stop smoking, if they so desired.

A scheme was devised, as will become apparent below, so that *both the number of cigarettes smoked per day as well as the amount of each cigarette smoked could be assessed.*

PROTOCOL OF THE TEST. The protocol of the tests was as follows:

One week served as control week. During that time, the subjects smoked as they pleased. Each cigarette smoked, when extinguished, was placed in a container, marked with the subject's name, cigarette brand, and day on test. These containers were collected daily, and a new container issued. Each subject pledged full cooperation for the duration of the test.

The second week was the placebo week. Each subject was given a quantity of placebo starch capsules. No subject, nor the dispensing technician was told the nature of the contents of the capsule, or even that it might or might not be a placebo. Each subject took 3 capsules per day, one after each meal. The collection of the discarded cigarettes was accomplished as outlined above.

TABLE 1.—COMPARISON BETWEEN NUMBER OF CIGARETTES SMOKED AND AMOUNT OF TOBACCO CONSUMED

A. *"No Wish to Stop" Group*

	Days on Test													
	1		2		3		4		5		6		7	
	No.	Wt.	No.	Wt.	No.	Wt.	No.	Wt.	No.	Wt.	No.	Wt.	No.	Wt.
Control week	18.3	11.9	18.2	12.9	17.7	12.6	18.4	10.3	18.1	12.1	17.9	11.4	18.4	11.5
Placebo week	17.8	12.4	18.0	11.7	18.1	12.8	17.9	12.0	17.8	11.8	18.0	10.4	17.7	11.5
(3-week wait period)	17.9	12.7	17.7	10.2	18.3	12.2	18.0	10.4	18.4	12.8	17.9	12.2	18.2	11.4
Control week														
Bantron week	16.5	10.7	17.2	8.3	17.4	6.7	18.1	4.2	17.9	5.4	18.0	5.0	17.7	4.1

No. = Average number of cigarettes smoked per day
Wt. = Average wt. of tobacco consumed in cigarettes smoked per day

B. *Group Desiring to Stop*

	Days on Test													
	1		2		3		4		5		6		7	
	No.	Wt.	No.	Wt.	No.	Wt.	No.	Wt.	No.	Wt.	No.	Wt.	No.	Wt.
Control week	19.4	12.0	18.6	11.6	18.3	11.8	17.9	10.8	18.3	11.7	18.4	12.3	18.6	11.1
Placebo week	18.8	10.7	17.5	10.2	16.2	9.8	15.7	11.4	16.3	11.6	16.4	10.8	16.8	11.2
(3-week wait period)	18.4	12.6	17.6	12.7	18.4	11.4	16.7	10.2	16.6	9.9	18.4	11.1	17.8	11.4
Control week														
Bantron week	17.9	10.4	14.2	8.6	7.5	6.4	5.3	4.2	4.8	3.9	5.2	4.1	4.6	4.5

There then followed a 3-week waiting period during which time no record of smoking was kept.

Then there followed another control week, as in the first week outlined above, when the smoked cigarettes were again collected.

This was followed by a Bantron week. The capsules, identical in appearance with the control capsules were given in a "double blind" basis again, neither the subject nor the dispenser knowing the nature of the capsule content. The used cigarettes were collected as above.

After the experiment had been concluded, all the cigarettes were counted and weighed in each container for each subject. One basic assumption was made: that each cigarette weighed exactly 1.0 gm. at the start. This figure may, of course, be in error, but is close enough for purposes of this experiment. To weigh each individual cigarette before and after use would have been a monumental task, not considered worth the time.

By counting the number of discarded cigarettes, and from the total weight remaining, a good estimate could be made of both the number of cigarettes smoked each day, as well as the amount of each cigarette smoked.

Results. These data are set forth in Table 1.

It can be seen from the Table that buffered lobeline has decreased the amount of smoking in both the "want to" as well as the "do not want to" groups.

This is clearly shown in the amount of cigarettes smoked, not in the number lit and partially smoked. Unless both sets of data are evaluated, erroneous conclusions may result.

Conclusions. From the evidence obtained in this study, and presented above, three conclusions seem justified:

1. Lobeline sulfate, suspended in corn starch as an inert vehicle, is not readily absorbed from the human gastrointestinal tract.

2. Lobeline sulfate in a buffered vehicle consisting of tricalcium phosphate and magnesium carbonate (referred to as the Bantron formulation), is absorbed from the human gastrointestinal tract readily and consistently.

3. The blood lobeline level established from the lobeline preparations is directly related to the effectiveness of this agent in acting as a curb to smoking. The effective level in the blood seems to be around 100 to 140 μg. lobeline per 100 ml. blood.

4. A subject *wishing to stop smoking* can do so, or at least cut down materially the number of cigarettes smoked per day, as well as the amount of each cigarette smoked.

5. A subject *not wishing to stop smoking*, might not cut down the number of cigarettes smoked per day, since that is determined in part by pure physical habit patterns and social custom. However, he will cut down the amount of each cigarette smoked, when using Bantron as indicated in this test. Such a subject apparently put most of the cigarettes out much sooner than he ordinarily would.

6. A count only of the number of cigarettes smoked per day seems not to be a valid criterion in evaluating the effectiveness of a regimen designed to aid in curbing smoking.

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(Interlingua on page 303)

SERUM HEPATITIS FROM WHOLE BLOOD: INCIDENCE AND RELATION TO SOURCE OF BLOOD

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The reported incidence of homologous serum hepatitis (S.H.) due to the transfusion of whole blood has varied, depending, among other things, upon the size of the population studied, the follow-up methods, diagnostic criteria used and the region in which the study was performed.

Screening procedures for blood donors now in use are based upon questionnaires designed to elicit a history of hepatitis, examination of the bilirubin content of the blood donated and occasionally the use of more refined techniques of estimating liver function (Jennings *et al.*[3], Loder[6]). These methods have the drawback of lack of specificity and dependence upon the hurried testament of the donor.

The present study was undertaken in 2 Veterans Administration hospitals in the Boston area to determine: 1) the incidence of S.H. during the years 1952 through 1957, 2) to compare this incidence with that reported in the literature by others and 3) to determine the relation between an apparent increase in incidence of S.H. noted in certain years and the purchase of whole blood from a particular commercial source. The study was undertaken when the occurrence of 7 cases of S.H. at one of the hospitals in a single year caused concern as to the possibility that the blood from this commercial source may have been responsible. The study was extended to the other hospital in order to test this hypothesis further. The Veterans Administration hospitals offer a unique opportunity to study the epidemiology of S.H. since their blood banks and clinical records are well kept and since the likelihood is great that a recipient of blood who subsequently develops S.H. will return to the same hospital for treatment.

The data presented below suggest that a single commercial source may have been responsible for much of the increased incidence noted during the years it served as a supplier.

Materials and Methods. The records of all cases diagnosed as S.H. from 1952 through June, 1957, at the West Roxbury (WRVA) and Boston (BVA) Veterans Administration hospitals were reviewed. Criteria for inclusion of a case in the study were: 1) evidence that the patient received transfusions of whole blood in the respective hospital within a period of 1½ to 6 months prior to the onset of jaundice. One case with an incubation period of 7 months was included because it presented a classical picture of the disease; 2) evidence that the patient did not receive transfusions or injections of pooled plasma or human thrombin during the incubation period; 3) clinical and laboratory evidence of hepatitis when chemical damage, metastatic tumor, nutritional disease or contact with cases of infectious hepatitis (I.H.) could not be implicated as the cause. Since patients receive many medications during their hospital stay, injections for therapeutic and diagnostic purposes could not be excluded as vehicles for the transmission of the S.H. virus.

The records of all cases diagnosed as I.H. at the BVA were reviewed to ascertain whether receipt of blood had been excluded. No additional cases of possible S.H. could be culled from this group. Furthermore, there were no patients who received blood at one hospital and were treated for S.H. at the other despite the close proximity of the 2 hospitals.

The serial numbers of the units of blood received and the dates as recorded in the patient's hospital record were compared with the blood bank records, and the origin of the blood was noted. They were then classified as having been received from volunteer donors at the respective hospitals (V.A.), the American Red Cross (R.C.), loans from other banks (included with V.A.) and commercial sources (Banks X, Y and Z). Bloods were considered as possibly infected only if they were administered within the incubation period noted above.

The records of each of the 2 hospitals were further reviewed and the number of pints of blood dispensed each fiscal year and the respective sources were ascertained. In addition, at the WRVA all recipients of blood during the fiscal years 1953 through 1956 were classified as having received blood 1) from bank X alone, 2) from multiple sources other than bank X, and 3) from multiple sources including bank X. The data are provided for each fiscal year which begins July 1 since contracts with commercial sources are awarded on this basis. All cases were assigned to the fiscal year in which the blood was received. The data for each hospital will be presented separately followed by a summary of the combined experience.

Results. WEST ROXBURY V.A. HOSPITAL. The records of 19 cases diagnosed as S.H. during the 4½ years covered by this study were reviewed. Thirteen of these cases met the criteria for inclusion in the study. All were males with ages ranging from 45 to 64 years. In Table 1 are listed total number of pints of blood used at that hospital, the number of cases of S.H., and the number of pints received by cases of S.H. in each fiscal year and according to the source of the blood. In addition, the per cent of total pints derived from each bank, the per cent of pints from each bank used in patients with S.H. and the cases of S.H. per 100 pints of blood used as derived from various sources are provided.

Sections A and B of Table 1 reveal that 4,361 pints of blood were given to patients during the study period at a rate of about 1,000 pints per year (1953 and 1957 are incomplete years). Bank V.A. and R.C. were represented each year to about the same extent and accounted for more than 2/3 of the total pints used. Bank X was used during 3 years and Bank Y during 2 different years. In sections C and D the number of cases of S.H. is listed for the fiscal years when they received the blood, and by the number of cases per 100 pints used from individual sources and from all sources. The greatest number of cases (10 1/3)* and the highest case rates (0.30 and 0.68) were noted in 1955 and 1956. During these years, bank X supplied about 20% of all blood used, bank Y was rarely used, while as noted above, banks V.A. and R.C. contributed their usual proportion of pints. In 1953 when Bank X provided more than 1/2 of the total number of pints used, only one case occurred, but 4 out of the 5 pints received by this case were from bank X. Of the 13 cases of S.H., 11 received some of their blood from bank X.

The data presented in section D indicate that although the case rate for all years and for all sources was 0.31, the case rate per 100 pints of bank X used was 1.37, irrespective of the number of pints from other sources. Sections E and F indicate that bank X not only contributed a greater number of pints than any other bank to cases of S.H., but that the per cent used in cases of S.H. per pint of bank X used in all recipients was higher than that

*One of the cases was split between 1954 and 1955 since 2 of the pints used in this case were received from bank Y in 1954 and one from bank X in 1955.

TABLE 1.—RELATION OF SOURCE OF BLOOD TO OCCURRENCE OF CASES OF SERUM HEPATITIS AT THE WEST ROXBURY V.A. HOSPITAL

Source of Blood	*Fiscal Year*					
	1953	*1954*	*1955*	*1956*	*1957**	*1953–1957**
	A. *Total Number of Pints Used*					
Bank						
X	307	5	217	229	0	758
Y	0	376	15	26	209	626
VA	133	422	426	341	126	1,448
RC	114	255	446	439	275	1,529
All Sources	554	1,058	1,104	1,035	610	4,361
	B. *Percent of Total Pints Derived from Each Source*					
Bank						
X	55.5	0.5	19.7	22.2	0	17.4
Y	0.0	35.6	0.2	0.3	34.2	14.4
VA	24.0	39.9	38.6	32.9	20.6	33.4
RC	20.5	24.0	40.4	42.4	45.0	35.1
All Sources	100.0	100.0	98.9	97.8	99.8	100.3
	C. *Number of Patients with S.H. Who Received Blood From Various Sources (Regardless of the Number from Other Sources)*					
Bank						
X	1	0	$3\frac{1}{3}$+	6	0	$10\frac{1}{3}$+
Y	0	$1\frac{2}{3}$+	1	0	0	$2\frac{2}{3}$+
VA	1	1	3	5	0	10
RC	0	0	2	4	0	6
All Sources	1	$1\frac{2}{3}$	$3\frac{1}{3}$	7	0	13
	D. *Number of Cases of S.H. per 100 pints of Blood from Various Sources (Regardless of the Number from Other Sources)*					
Bank						
X	0.37	0	1.54	2.62	0	1.37
Y	0	0.44	6.7	0	0	0.43
VA	0.75	0.24	0.71	1.47	0	0.69
RC	0	0	0.45	0.91	0	0.39
All Sources	0.18	0.16	0.30	0.68	0	0.31
	E. *Number of Pints from Each Source Used in Patients With S.H. (Regardless of Number from Other Sources)*					
Bank						
X	4	0	7	20	0	31
Y	0	2	2	0	0	4
VA	1	1	13	6	0	21
RC	0	0	11	10	0	21
All Sources	5	3	33	36	0	77
	F. *Percent of Pints from Each Source Used in Patients With S.H. (Regardless of Number from Other Sources)*					
Bank						
X	1.3	0.0	3.5	9.0	0.0	4.0
Y	0.0	0.5	13.3	0.0	0.0	0.6
VA	0.8	0.2	3.1	1.8	0.0	1.5
RC	0.0	0.0	2.5	2.3	0.0	1.4
All Sources	0.9	0.3	3.0	3.5	0.0	1.8

*First 6 months of fiscal year. +In one case 2 pints (non-Bank X) were received in 1954, and 1 pint of Bank X was received in 1955.

of any other bank or for all sources. Thus the blood received from bank X is more highly represented among the cases of S.H. than that from any other bank or from all other banks when compared with what would be expected from the amount of blood given to all recipients.

These data suggest a relation between the use of bank X blood and the increased number of cases. This alone, however, hardly constitutes a case against bank X since the correlation is imperfect, and since the patients with serum hepatitis generally received blood from multiple sources and only a small number of cases and of pints of blood were involved.

also serves to demonstrate that most individuals received blood from multiple sources and that there were very few individuals who received blood from single sources.

The data for the WRVA are inadequate for statistical analysis. The relation between bank X and cases of S.H. seemed intriguing nonetheless and stimulated an analysis of cases and of the blood used in a hospital in which as much blood was used in 1 year as in 4 at the WRVA.

BOSTON V.A. HOSPITAL. The records of 49 cases diagnosed as S.H. during period of 5½ years were reviewed; 24 of them met the criteria for inclusion in the study, most of the others being

TABLE 2.—COMPARISON OF BANK X AND ALL OTHERS AS A SOURCE OF CASES OF SERUM HEPATITIS AT THE WEST ROXBURY V.A. HOSPITAL 1953–1956

Source of Blood	*No. Pints Used*	*No. Cases S.H.*	*Cases S.H. per 100 Pints Used*	*No. Recipients of Blood*	*No. of Pints per Recipient*	*% Bank X Used*
X Alone	161	1	0.6	93	1.73	100
Multiple Without X	1,009	2	0.2	416	2.3	0
Multiple With X	1,388	10	0.7	172	8.1	37.3
All Sources	2,558	13	0.5	681	3.75	26.6

Table 2 provides a comparison for the years 1953–1956 of recipients of blood from bank X alone, and from multiple sources, with and without bank X, and with the number of cases of S.H. among these recipients. These data were gathered to circumvent the problem of multiple sources of blood given to cases of S.H. Analysis of these data is not possible because of the small number of cases. The table is therefore presented to demonstrate some of the difficulties in interpretation of this type of data. The number of cases and pints used is small and the number of pints per recipient is variable for each category. Thus, case rates calculated from such data, although suggesting that bank X was culpable do not clearly prove this. The table

excluded because they had either received their blood elsewhere or were considered to have developed their illness following the use of syringes. Two patients were excluded although they had received their blood during the appropriate interval; one had recurrent disease in the region of the common bile duct, died of fulminant hepatic disease and no necropsy was obtained; the other had carcinoma of the larynx with demonstrable metastasis to the liver at necropsy. The 24 patients ranged in age from 24 to 70 years and all but one were males.

Table 3 presents the data from the Boston V.A. Hospital in a manner similar to that shown in Table 1. The highest incidence of S.H. was noted in 1953 when 11 cases occurred, with a

TABLE 3.—RELATION OF SOURCE OF BLOOD TO OCCURRENCE OF CASES OF SERUM HEPATITIS AT THE BOSTON V.A. HOSPITAL

Source of Blood	*Fiscal Year*						
	1952	*1953*	*1954*	*1955*	*1956*	*1957**	*1952–1957**
	A. *Total Number of Pints Used*						
Bank							
X	589	1,468	0	0	0	0	2,057
Y	0	0	1,527	0	1,134	806	3,467
Z	0	0	0	1,015	0	0	1,015
VA	918	949	1,241	1,174	951	415	5,648
RC	1,779	1,473	1,312	2,085	1,683	723	9,055
All Sources	3,286	3,890	4,080	4,274	3,768	1,944	21,242
	B. *Per cent of Total Pints Derived From Each Source*						
Bank							
X	17.9	37.7	0	0	0	0	9.7
Y	0	0	37.4	0	30.1	41.5	16.3
Z	0	0	0	23.7	0	0	4.8
VA	27.9	24.4	30.4	27.5	25.2	21.3	26.6
RC	54.1	37.9	32.2	48.8	44.7	37.2	42.6
All Sources	99.9	100.0	100.0	100.0	100.0	100.0	100.0
	C. *No. Patients with S.H. Who Received Blood from Various Sources (Regardless of the Number from Other Sources)*						
Bank							
X	4	10	0	0	0	0	14
Y	0	0	1	1	3	0	5
Z	0	0	0	2	0	0	2
VA	2	7	1	3	0	0	13
RC	4	7	1	3	2	0	17
All Sources	4	11	1	5	3	0	24
	D. *No. of Cases of S.H. per 100 Pints of Blood from Various Sources (Regardless of the Number from Other Sources)*						
Bank							
X	0.67	0.68	0	0	0	0	0.68
Y	0	0	0.06	+	0.26	0	0.14
Z	0	0	0	0.19	0	0	0.19
VA	0.21	0.73	0.08	0.25	0	0	0.23
RC	0.22	0.47	0.07	0.14	0.11	0	0.18
All Sources	0.12	0.28	0.02	0.11	0.07	0	0.11
	E. *Number of Pints from Each Source Used in Patients with S.H. (Regardless of the Number from Other Sources)*						
Bank							
X	14	44	0	0	0	0	58
Y	0	0	1	2	9	0	12
Z	0	0	0	3	0	0	3
VA	11	16	1	8	0	0	36
RC	13	20	1	18	6	0	58
All Sources	38	80	3	31	15	0	167
	F. *Per cent of Pints from Each Source Used in Patients with S.H. (Regardless of the Number from Other Sources)*						
Bank							
X	2.4	3.0	0	0	0	0	2.8
Y	0	0	<0.1	+	0.8	0	0.4
Z	0	0	0	0.3	0	0	0.3
VA	1.2	1.7	<0.1	0.7	0	0	0.6
RC	0.7	1.4	<0.1	0.9	0.4	0	0.6
All Sources	1.2	2.1	<0.1	0.7	0.4	0	0.8

*First 6 months of fiscal year.
+Very few pints Bank Y blood used in 1955, total included with Bank Z.

rate of 0.28 cases per 100 pints of blood used. Fifteen of the 24 cases recorded occurred in 1952 and 1953 when bank X was the sole commercial source. In 1955 another commercial bank (Z) from the same city as bank X was used; 2 of the 5 cases ascribable to blood given in that year received blood from this source, and it was the sole source for one of those 2 cases. Sections A and B of Table 3 listing the number and per cent of pints used each year for each source and for all sources reveals that between 3 and 4 thousand pints of blood were used each year. Bank X was used only during the years of high incidence, 1952 and 1953. The per cent of bank X used rose from 17.9 in 1952 to 37.7 in 1953 while the case rate rose proportionally from 0.12 to 0.28 per 100 pints used. Bank Y was not used during any of the years of increased incidence. Bank Z was used in moderate amounts only in 1955 and its contribution to cases has been commented upon. The V.A. and R.C. banks, as in the WRVA experience, accounted for more than 2/3 of all pints used and contributed about the same amount of blood each year. Thus, the increased incidence of S.H. noted was best correlated with the use of bank X blood.

Sections C and D of this table list the number and per cent of cases of S.H. in relation to the source of their blood. Bank X was used in 14 of the 24 cases. Three of these cases received only bank X blood. The case rate for recipients of bank X blood per 100 pints of bank X used was 0.68 as opposed to 0.11 for cases from all sources per 100 pints given to all recipients from all sources. Bank X is represented in this regard to a greater extent than any other bank.

In sections E and F it can be noted that bank X and R.C. contributed the largest number of pints to patients with S.H.; however, bank X contributed a larger proportion of the pints given to cases of S.H. than did the blood from all sources including bank R.C. Thus not only did the use of bank X coincide more closely in time with the appearance of an increased number of cases, but the amount from this bank that was used in cases of S.H. was proportionally greater than that given to all recipients from any other source or from all sources.

COMBINED EXPERIENCE. Table 4 presents a summary of the combined experience of the 2 hospitals. The pooling of these data is considered valid because the 2 hospitals were administered in a similar fashion, kept records in an identical manner, were studied in about the same years, derived their blood from similar sources, provided medical care to the same groups of people and are located in the same area. This table is divided into 3 sections. Part A includes the periods when bank X was used as the commercial source of blood, B includes the periods when bank X was not used as the commercial source, and the total experience for all fiscal years is shown in part C. During the periods when bank X was used, it provided about 30% of the blood given to all recipients in each hospital. During these years the number of cases per 100 pints used was 3 to 4 times as high as during years when bank X was not used. In the total experience, the case rate at the WRVA was almost 3 times as high as that at the BVA, but the BVA received 9.7% of its blood from bank X whereas the WRVA received almost twice this percentage of bank X blood.

Using the Chi Square test, determining the number of expected cases on the basis of the number of pints used and assuming the same distribution of pints per recipient for each and all banks, the differences noted in the case rate for the BVA between years

that bank X was and was not used is significant ($P = .01$). The difference for the WRVA is not significant ($P = >.05$), while that for the combined experience is of borderline significance ($P = .05$).

Bank X blood was used in 1954, 1955 and 1956 at the WRVA and in 1952 and 1953 at the BVA. There is overlap in the years of usage in 1953, but the span of years extends from 1952 through 1956 for both hospitals. This other sources. A record of icteric pints was not kept at the WRVA, but technicians there recall having received and discarded icteric pints from bank X, but not from other sources.

REPORTED INCIDENCE OF SERUM HEPATITIS. An attempt was made to determine the incidence of serum hepatitis in relation to blood transfusions as reported in the literature. In most of the earlier reports the data presented are for combinations of plasma and whole

TABLE 4.—TOTAL EXPERIENCE WITH SERUM HEPATITIS AT TWO HOSPITALS IN RELATION TO THE USE OF BLOOD FROM BANK X

Hospital	*Pints Used*	*No. Cases*	*Cases per 100 Pints Used*	*No. Pints Bank X Used*	*% Pints Bank X Used*
	A. *Experience During Fiscal Years When Bank X Was Used*				
B.V.A.	7,176	15	0.21	2,057	28.7
W.R.V.A.	2,693	11⅓*	0.42	753	28.0
Total	9,869	26⅓*	0.27	2,810	28.5
	B. *Experience During Fiscal Years When Bank X Was Not Used*				
B.V.A.	14,066	9	0.06	0	0.0
W.R.V.A.	1,688	1⅔*	0.10	5	0.3
Total	15,754	10⅔*	0.07	5	0.03
	C. *Total Experience During All Fiscal Years of the Study*				
B.V.A.	21,242	24	0.11	2,057	9.7
W.R.V.A.	4,361	13	0.31	758	17.4
Total	25,603	37	0.14	2,815	11.0

*In one case of S.H. 2 pints (non-Bank X) were received in fiscal 1954, and 1 pint (Bank X) was received in fiscal 1955.

reduces the likelihood that the increased incidence noted could be attributed to an unusual incidence of I.H. in any single year.

STATUS OF PINTS DELIVERED. No systematic study was performed to analyze the incidence of abnormal liver function tests in all the individual bloods used in either hospital. The records of the BVA, however, list 4 pints of bank X blood received in fiscal year 1953 which were icteric on inspection and discarded. Two pints of blood from R.C. delivered in 1954 were also grossly icteric and discarded. No similar observations were recorded in pints from blood. Frequently, the number of recipients is noted without concurrent data on the amount of blood used. Some surveys have been made by postal inquiries and by house and clinic visits, and some authors excluded patients who died within the incubation period while others did not make this adjustment as it was necessary to do in the present report.

The study of Scheinberg, Kinney and Janeway[9] was the most comprehensive reported in the Boston area, but since both plasma and whole blood were used, a valid comparison cannot be made of their incidence of 0.45 cases

TABLE 5.—REPORTED INCIDENCE OF HOMOLOGOUS SERUM HEPATITIS DUE TO WHOLE BLOOD TRANSFUSIONS

Author	*Country and Date of Study*	*No. of Persons Studied*	*Total No. of Units Used*	*Mean No. of Units/Person*	*No. of Cases of S.H.*	*Cases of S.H. /100 Recipients*	*Cases of S.H. /100 Units Used*
Spurling *et al.*[10]	Great Britain 1944	891	2,278	2.6	0*	0.0	0.0
Lehane *et al.*[5]	Great Britain 1945–1948	2,796	6,210	2.2	22	0.8	0.35
McGraw *et al.*[8]	U.S.A. 1943–1947	382	764**	2§	1† 1‡	0.26† 0.52†‡	0.13† 0.26†‡
Hässig *et al.*[2]	Switzerland 1950–1951	189	635	3.4	1	0.53	0.16
Allen *et al.*[1]	U.S.A. 1942–1953	10,610	37,026	3.5	39	0.37	0.11
Allen *et al.*[1]	U.S.A. Survey 124 blood banks	—	1,248,439	—	544	—	0.04
Madsen[7]	Denmark 1951	554	1,430	2.6	6	1.1	0.42
Katz *et al.*[4]	Chile	144	398	2.8	6	4.16	1.51
Jennings *et al.*[3]	U.S.A. 1954	796	2,475	3.1	10	1.26	0.40
Loder[6]	U.S.A. 1954–1955	—	1,015	—	3	—	0.30
W.R.V.A.	U.S.A. 1953–1957	—	4,361	—	13	—	0.31
B.V.A.	U.S.A. 1952–1957	—	25,603	—	24	—	0.11

* There were 6 cases of jaundice which for various reasons were unacceptable to the authors as S.H.
**Estimation from data on mean pints per person.
§ Reconstructed from data provided.
† Probable
‡ Possible

of S.H. per 100 units administered and that found in the present study.

Table 5 presents a series of reports from the literature together with the data obtained in the present study. These data were selected on the following basis: the number of units of whole blood used was provided, plasma was not used, and a reasonably large experience was presented. The number of cases per 100 pints used is considered a more significant attack rate than is the number of cases per 100 recipients since, with the exception of pints given to cases of S.H., all others used may be considered nonicterogenic, regardless of the number of pints per recipient. Since the number of pints given to patients who subsequently develop S.H. is small and the frequency of infected pints is low, the probability that icterogenic pints may be missed in these cases is small.

Five countries are represented in this table with an experience extending from 1942 to 1957. Of greatest interest for comparative purposes is the last column of this table in which the cases of S.H. per 100 units of whole blood used are listed. The lowest incidence was that reported by Spurling, Shone and Vaughan[10] in Great Britain, where no acceptable cases occurred following over 2,000 transfusions. The highest incidence is noted in Chile (Katz *et al.*[4]) where the rate was 1.51 per 100 units administered; that country is considered to have a high endemicity of S.H. for reasons that are not apparent. The experience of Allen *et al.*[1] in reporting the responses to questionnaires of 124 blood banks involving more than 1 million pints of blood is of interest. The case rate was quite low, 0.04 per 100 units used, and this was undoubtedly due to the inadequate follow-up methods used by so many banks; the incidence in their own blood bank was 3 times as high. In general, the rates reported were less than 1.0% except for the experience in Chile. The data presented in the current report of 0.11 and 0.31 cases per 100 pints fall well within the range reported by others.

Discussion. This study was undertaken to determine whether or not an apparent increase in the incidence of homologous serum hepatitis noted during a single year at the West Roxbury V.A. Hospital was due primarily to the use of blood from a single commercial source. A retrospective study was made, utilizing the hospital records of cases occurring during a 5-year period and of all pints used during that period. Data obtained in this manner suggested the possibility that one commercial source may indeed have been responsible for more than its expected share of cases.

Two lines of evidence were available; the temporal relation of an increased number of cases during years in which this bank was the commercial source and an unexpected representation of pints of blood from this bank in patients who subsequently developed hepatitis. Neither of these lines of evidence was conclusive.

A similar study was, therefore, undertaken at the Boston V.A. Hospital during a 6-year period; this hospital had received its blood from similar sources. Once again an unexpected representation of pints from the suspect bank was found in cases of S.H. This time a comparison of the incidence of cases per 100 units during the years used when bank X supplied 28.5% of all pints used and the years when a negligible amount was used revealed a difference in the attack rates significant at the 0.01 level. The comparison for both hospitals on a similar basis was of borderline significance ($P = .05$).

The following assumptions have been made which are considered to be

valid for this type of comparison: 1) a representative proportion of cases of S.H. receiving blood from each source reported back to each hospital for diagnosis and treatment; 2) all cases included were truly S.H. resulting from transfusion of blood; 3) cases of S.H. occurring from needles, syringes and blood products were negligible or were balanced out; 4) the most valid estimate of the number of icterogenic pints used when multiple transfusions are given is based on the number of cases per 100 pints of blood given, regardless of the number of pints received by the individual recipients; 5) the number of icterogenic pints missed in patients dying during the incubation period was negligible or balanced out; 6) a single pint was responsible for each case and the remaining pints received were not icterogenic. This final assumption appears to be valid in view of the small number of pints given to cases and the low overall incidence of the disease.

The data in this report indicate that blood derived from a single commercial source was responsible for a small but significantly higher incidence of hepatitis than that which occurred from other sources. Since this bank provided only 11% of all pints used in both hospitals, its true potential for producing cases of S.H. was largely masked. This finding together with the presence of 4 icteric pints in a single year's shipment from the offending bank indicates not only that inadequate methods of donor screening were used, but that the population serving as donors for that bank may well have a higher than usual incidence of S.H. Obviously the policies of such a bank need to be reviewed; until then limited use should be made of blood from this source.

The Veterans Administration hospitals offer a unique opportunity to study the epidemiology of S.H. because of excellent patient and blood bank records and follow-up facilities. Studies designed to detect high incidence sources, to evaluate screening procedures and methods of blood sterilization can be performed with relative ease and reliability. The data provided in this report may serve as a basis for the expected incidence of cases and for rational planning of such programs.

Summary. The data on the incidence of homologous serum hepatitis at 2 Veterans Administration hospitals in the Boston area during a 6-year period have been presented. The relation of a single commercial source of blood to an increased incidence of S.H. during years in which it was used has been outlined. This relation implies either inadequate screening methods on the part of this bank or the procurement of blood from a population with an unusually high incidence of carriers, or both. It is suggested that the use of blood from this bank should be curtailed until its procedures are reviewed and corrected.

ACKNOWLEDGMENTS: I am indebted to Dr. Thomas Warthin of the West Roxbury V.A. Hospital for making the initial observations which stimulated this study and to Dr. Eugene Sullivan for permission to review the records of the Boston V. A. Hospital; to Margaret Drolette of the Harvard School of Public Health for aid in the statistical analysis; and to Dr. Maxwell Finland for his help in the preparation of the manuscript.

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SUMMARIO IN INTERLINGUA

Hepatitis Del Typo Sero-Homologe, Causate Per Sanguine Integre: Incidentia E Relation Al Provenientia Del Sanguine

Es presentate datos relative al incidentia de hepatitis del typo sero-homologe a 2 hospitales del Administration de Veteranos in le area de Boston durante un periodo de 6 annos. Le relation de un unic fonte commercial de sanguine con un augmento del incidentia de hepatitis del typo sero-homologe durante le annos quando ille fonte esseva utilisate es delineate. Iste relation indica (1) inadequate methodos de selection del parte del banca o (2) le obtention del sanguine ab un population con un inusualmente alte incidentia de portatores o (3) le presentia de ille duo factores in combination. Es proponite que le uso de sanguine ab le banca in question deberea esser reducite usque su methodos ha essite investigate e corrigite.

SUMMARIO IN INTERLINGUA

(See page 287 for original article)

Le Absorption De Lobelina E Su Utilitate Como Deterrente Pro Fumatores De Tabaco

Super le base del datos colligite in le presente studio, le sequente conclusiones pare justificate:

1. Sulfato de lobelina, suspendite in amylo de mais como vehiculo inerte, non se absorbe prestemente ab le vias gastrointestinal del homine.

2. Sulfato de lobelina in un vehiculo tamponate, consistente de phosphato tricalcic e carbonato de magnesium e designate como le formula Bantron, se absorbe preste- e uniformente ab le vias gastrointestinal del homine.

3. Le nivello sanguinee de lobelina que resulta ab le preparatos de lobelina es directemente relationate con le efficacia de iste agente in restringer le habitude del fumar. Le efficace nivello sanguinee pare esser in le vicinitate de 100 a 140 μg de lobelina per 100 ml de sanguine.

4. Un subjecto *qui desira cessar su fumar* pote facer lo. Al minus, ille pote reducer considerabilemente le numero de cigarrettas consumite per die e etiam le portion consumite de omne cigarretta individual.

5. Un subjecto *qui non desira cessar su fumar* probabilemente non reduce le numero del cigarrettas consumite per die, proque isto es determinate in parte per constellationes de habitudes physic e de costumes social. Tamen, ille reduce le portion consumite de omne cigarretta individual quando illo usa Bantron como indicate in iste test. Il pare que un tal subjecto extingue le majoritate de su cigarrettas multo plus promptemente que esseva su habitude previemente.

6. Il pare que contar simplemente le numero de cigarrettas consumite per die non produce un valide criterio in evalutar le efficacia de un regime per que on vole restringer le habitude del fumar.

LESS COMMONLY RECOGNIZED ACTIONS OF ATROPINE ON CARDIAC RHYTHM

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Atropine sulfate is a well known peripheral parasympatholytic blocking agent. When it more or less completely blocks the vagus nerve cardiovascular effects are rather constant. Acceleration in heart rate is the consistently reproducible phenomenon with both oral and parenteral administration. Other changes in cardiac rate, rhythm, and conduction are not generally appreciated or have been subject to conflicting interpretations by a number of investigators. This paper will discuss briefly the more important atropine-induced electrocardiographic changes other than atropine tachycardia. The value of being familiar with these interesting changes and the application of this knowledge in both clinical and investigative cardiology will be pointed out.

The clinical use of atropine in cardiology is well established. Patients who have complete atrio-ventricular block and episodes of ventricular standstill may benefit from divided daily doses of atropine. One must, however, exclude so-called "Adams-Stokes" episodes which are due to ventricular tachycardia and ventricular fibrillation rather than ventricular standstill or marked transient bradycardia. The vagolytic effect of atropine upon the heart is useful in acute myocardial infarction when bradycardia of severe degree develops. Atropine may also be used to advantage in patients with acute myocardial infarction receiving drugs which have a vagotonic effect such as digitalis, quinidine or procaine amide. Atropine decreases undesirable depressant action on the A–V conduction system.

Schwartz states that in patients with established complete A–V block atropine will increase both the atrial and ventricular rates showing that the idioventricular pacemaker is at all times under the influence of the extrinsic nerves of the heart (Schwartz and Pool[17]). He has further shown that atropine will abolish premature ventricular contractions in some patients with complete A–V block who are subject to transient periods of ventricular fibrillation. Perhaps in these patients atropine may decrease the seizures of transitory ventricular fibrillation.

Prior to atropine induced tachycardia a pre-blockage vagal stimulation may be seen causing transient cardiac slowing. The exact nature of this phenomenon is not known (Goodman and Gilman[4], Levin[9], Lewis[10], McGuigan[11], Nalefski and Brown[12], Rudolph and Bulmer[16], von Annep[18]). There has been speculation that it might be caused by central vagal stimulation.

Observations have been made on the effects of atropine on the PR interval.

Atropine frequently causes shortening of the PR interval, both when it is initially normal and when initially prolonged (Graettinger[5]). Atropine-induced shortening of the PR interval is of no diagnostic value in differentiating between the various causes of such a prolonged interval (Robinson[15]).

Materials and Methods. Atropine sulfate, 0.8 or 1.2 mg., was administered intravenously to 60 cases being evaluated for a clinical syncopal episode, 50 normal aviation cadets serving as controls for evaluation of syncopal reactions, and routinely to over one hundred consultation problems of cardiac arrhythmias, including Wolff-Parkinson-White syndrome, atrial rhythm, bundle branch block, premature contractions and others. From these records representative tracings have been selected to illustrate various actions of atropine.

Observations and Discussion. There is a rather well-defined period after the intravenous administration of atropine sulfate (0.8 to 1.2 mg.) when very interesting rhythm and conduction changes may be seen. This time period lies between 30 seconds and 90 seconds following the rapid intravenous injection of atropine. Consequently a continuous electrocardiogram is necessary from the instant of injection to the establishment of full atropinization or these changes will be missed. The critical time period for a similar phase after the subcutaneous administration of atropine sulfate (0.8 to 1.2 mg.) varies between 15 and 30 minutes, depending on the rate of absorption. Because of the variability in absorption the subcutaneous route is not as useful in studying this particular phenomenon of atropine activity.

SIMPLE A–V DISSOCIATION. The most common change in the early action following intravenous atropine sulfate is A–V dissociation with interference. The atria are being stimulated by one focus and the ventricles by another.

Simple A–V dissociation with interference following the intravenous administration of 0.8 mg. of sulfate is shown in Fig. 1. In this case the 8th P wave on the top line is late in appearance and the A–V node escapes beginning a period of A–V dissociation. The P wave moves in and out of the QRS complex. It remains upright, proving that retrograde conduction to the atria from the A–V node does not take place. The 4th and 5th complexes in the bottom row are instances of ventricular capture by the atria. Capture of the atria by the ventricles in A–V dissociation following atropine has not been observed.

Physiological interference to transmitted impulses at the A–V node, due to the normal refractory periods of the tissues, is responsible for maintaining A–V dissociation, and does not allow the atria to capture the ventricles nor the atria to be stimulated by retrograde action from the A–V node. The ventricular rate is equal to or slightly faster than the atrial rate.

Transitory A–V dissociation after atropinization was recognized first by Wilson[19] in 1915 after the subcutaneous administration of atropine. Wilson did not recognize the type of A–V dissociation which occurred, thinking it was A–V nodal rhythm with retrograde conduction to the atria. A review of the published tracings, however, shows that this was not the case and that A–V dissociation with interference was present in his cases with the exception of 2 patients in whom a lower nodal rhythm was present. The A–V dissociation in these patients occurred 8 to 20 minutes following subcutaneous atropine (1 mg.). This was during the period when full atropinization was not present.

The changes in rhythm occurred spontaneously in only a few of his patients. In the majority he induced the change by stimulating the vagal tone

by ocular pressure, carotid sinus pressure and by various respiratory maneuvers. This would produce a further imbalance in the sub-maximal atropinized state and support the hypothesis that has been advanced for the spontaneous occurrence of A–V dissociation following atropine. This hypothesis is that, in the period between the vagotonic effect of atropine and complete atropinization, an imbalance in the magnitude of effect exists at the various levels of the conduction system.

travenous injection. Although subsequent tracings were taken at various intervals for one hour the intravenous effects would not be present and the changes seen after injection by the subcutaneous route are difficult to pick up as mentioned previously.

A–V dissociation with interference will usually occur 30 to 90 seconds following intravenous atropine if it is going to occur at all. It may persist for only a few heart cycles or for 2 to 3 minutes either continually or inter-

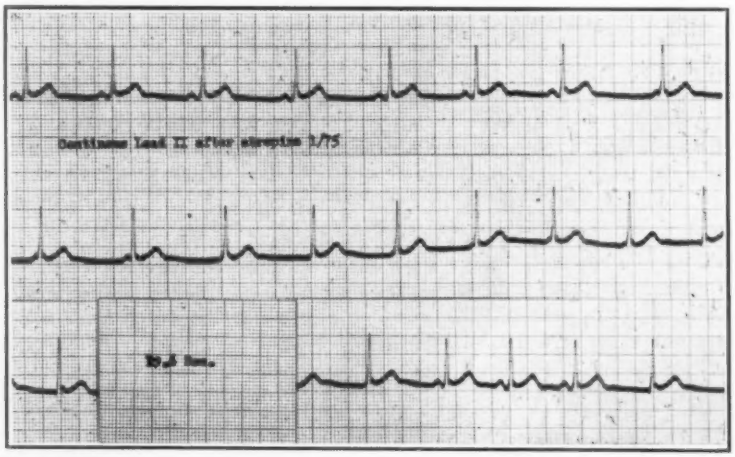

Fig. 1.—Simple A–V dissociation with interference following atropine intravenously. The 8th P wave is delayed and a nodal escape beat initiates the A–V dissociation.

Nalefski and Brown[12] gave atropine sulfate (0.2 mg. per kg.) either subcutaneously or intravenously to 133 subjects and observed changes in rate, blood pressure, and in the electrocardiogram. They state that no changes were noted in the electrocardiogram other than changes in rate and some small changes in voltage of the QRS complexes. This failure to note significant electrocardiographic changes is no doubt due to the fact that the first post-atropine tracing was not done until 4 minutes after injection, too late for the transitory changes following intermittently. In a few instances it may persist for longer periods of time.

Inspection of a large number of tracings in which A–V dissociation with interference has followed atropine administration has demonstrated two different patterns of onset. In some instances the dissociation occurs with sinus slowing, allowing the A–V node to assume the role of pacemaker for the ventricles in a passive manner. In other instances there is no sinus slowing at the onset of A–V dissociation. The A–V node suddenly begins discharging at a rate slightly faster than

the supra-nodal focus and captures the ventricles in an ectopic manner. Physiologic interference then perpetuates the A–V dissociation for a variable period of time in both cases.

The onset of A–V dissociation may be related to individual differences in the balance between the early vagotonic effect of atropine depressing the supra-nodal focus and an early selective action of the anticholinergic effect of atropine on the ventricular conduction system. Wilson in 1915[19] explained the production of A–V dissociation with interference by saying: "We believe the special susceptibility of the heart toward A–V rhythm (A–V dissociation with interference) during the early action of atropine is due to a selective action of the drug on the vagus terminations in the A–V node, in that it paralyzes these fibers before it paralyzes those in the sinus node."

It has been interesting to compare the changes associated with the early action of atropine to some noted when the vagus nerve is stimulated by various means. Of particular interest are the effects of certain respiratory maneuvers on the heart. Wilson[20] in 1915 described the production of a shift in the cardiac pacemaker from the S–A node to the atria in one case, to a true upper nodal rhythm in another, and A–V dissociation with interference in still another following simple respiratory maneuvers. Recently further observations have been made on the cardiac effects of these maneuvers (Lamb, Dermksian and Sarnoff[18]). The term "pulmonary stretch reflex" has been used to describe the effect on vagal afferent endings in the lungs which causes impulses to pass to the central nervous system and thence by way of vagal efferent fibers to the heart. Marked changes in vagal tone are produced. Cardio-inhibitory phenomena have been noted repeatedly. Equally interesting has been the occurrence of A–V dissociation with interference, A–V nodal rhythm, atrial rhythm, and various conduction defects at the A–V node. These changes are very similar to those seen in the early phase of atropine activity. Selective vagal influence by vagal stimulation and selective decreased vagal influence by partial atropinization thus produce changes in cardiac rhythm and conduction which are similar during the period of vagal imbalance.

A–V DISSOCIATION AND SYNCHRONIZATION. The phenomenon of "synchronization" is common during A–V dissociation following atropine. Synchronization is present when the ventricles and atria are beating simultaneously although each is stimulated by a different focus. The P waves of atrial excitation are lost in the QRS complexes of ventricular excitation. Synchronization is particularly interesting when one sees the heart rate increase during and at the time the P waves remain hidden in the QRS complexes. This indicates that although the atria and ventricles are stimulated by completely different foci, both foci are in some manner tuned to each other so that an increase in rate of one pacemaker is accompanied by a corresponding increase in the other. Synchronization may persist for only a few beats or for as long as a minute before the P wave moves out of the QRS complex, indicating a change in either the atrial or ventricular rate.

Synchronization and an apparent early vagal effect of atropine at the A–V node are both demonstrated in Fig. 2. Prior to the injection of atropine the cardiac rate was approximately 44 per minute. Immediately after 0.8 mg. atropine sulfate intravenously the rate slowed to 37 to 39 per minute (not shown). The cardiac rate then slowly increased, and, as it did so, the PR

interval became prolonged from .20 sec. to .26 sec. It is interesting in this instance that the early vagotonic effects of atropine on the cardiac rate and the A–V node did not coincide. Prolonged conduction at the A–V node did not disappeared. This change did not take place in a passive manner following slowing of the sinus node as demonstrated in Fig. 1 but by early discharge of the A–V node, representing its selective escape from vagal control during

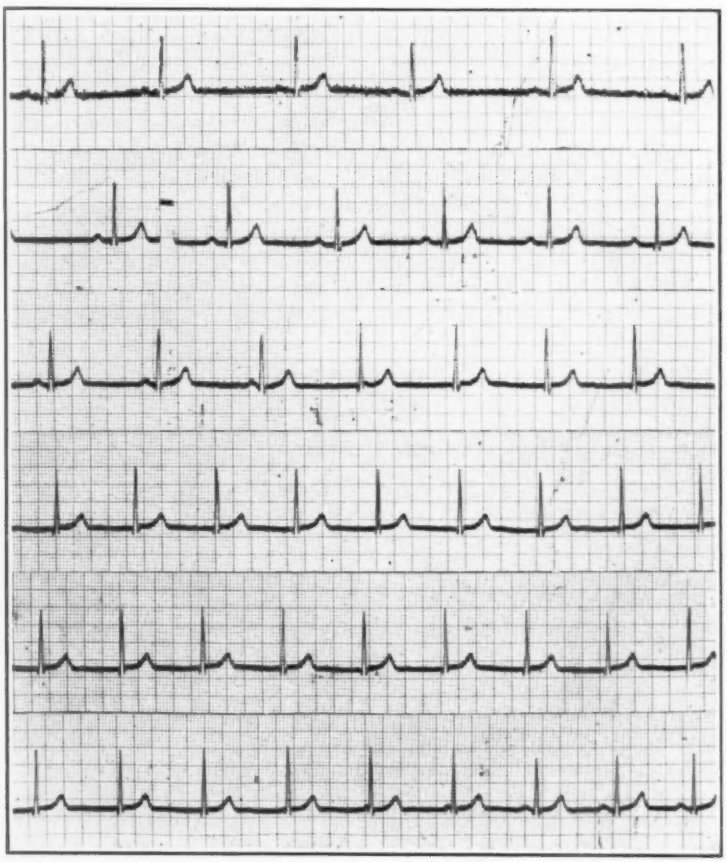

Fig. 2.—A–V dissociation with interference, synchronization, and an apparent early vagotonic effect following intravenous atropine sulfate. Primary escape of the A–V node rather than sinus slowing initiates the A–V dissociation in this instance.

occur until after the early vagotonic effect of atropine on the heart rate had disappeared. The PR interval then decreased slowly, and, prior to A–V dissociation (3rd strip), was .16 sec. As A–V dissociation occurred the P wave moved into the QRS complex and early atropinization. A–V dissociation is perpetuated by physiological interference.

Synchronization takes place and persisted for 30 seconds. Although the cardiac rate increased from 56 to 65 per minute during synchronization, the

P wave remained hidden in the QRS complex. One might be inclined to call this period a middle nodal rhythm with retrograde conduction to the atria but obvious upright P waves moving into the QRS complexes at the onset and out of the QRS complexes at the end of the A–V dissociation support the impression that retrograde conduction to the atria did not take place during the period of synchronization. At the termination of synchronization A–V nodal discharge remained constant as the S–A node began to discharge more rapidly and finally stimulated the atria well in advance of the A–V node so that ventricular capture by the atria occurred. A normal sinus rhythm developed at a rate faster than either the previous atrial or ventricular rate.

A–V DISSOCIATION AND LOWER ATRIAL RHYTHM. Those arrhythymias which show an inverted P wave in Leads II and III with a P–R interval of over .10 sec. are of particular interest. The negative P waves denote retrograde excitation of the atria. This rhythm is commonly called an upper nodal rhythm with retrograde excitation of the atria and retrograde block. This study included a thorough investigation of a number of healthy, young pilots who have demonstrated this electrocardiographic pattern. We have preferred to consider these rhythms as originating from a low atrial focus rather than from the A–V node with retrograde conduction. With a P–R interval of over .10 sec. one would have to postulate that these asymptomatic young men have both an A–V nodal rhythm and, in each case, retrograde incomplete block. This is highly unlikely. A more appealing explanation is that a low lying atrial focus is the cardiac pacemaker causing retrograde conduction to the atria, but because of its distance from the A–V node, the PR interval is greater than .10 sec. The interval is usually between .12 sec. and .14 sec. which falls within normal limits.

Lead II of the baseline record from a patient with an intermittent abnormal rhythm of negative P waves in leads II and III is seen in Fig. 3. Ten minutes after breathing 100% oxygen under normal atmospheric pressure he was found to have the abnormal supraventricular rhythm. The P–R interval was .12 sec. The question arises whether this is A–V nodal rhythm with retrograde block, or whether this is a simple passive atrial rhythm from an atrial focus. He was given 1.2 mg. atropine sulfate intravenously. Seventy-five seconds later definite A–V dissociation was seen. Note in Fig. 3 (third strip) how the P wave moves into the QRS complex. If one considered the negative P wave to be the result of retrograde conduction from an upper nodal rhythm then one would have to assume interference occurring within the A–V node itself during the A–V dissociation. Thus the upper portion of the A–V node would be controlling the atria while some other part of the A–V node controlled the ventricles. It is difficult to accept this explanation. The more logical explanation would be that the initial rhythm was atrial in origin and that following A–V dissociation the atria are stimulated by the atrial focus and the ventricles stimulated by the A–V node. A third explanation might be put forth that this rhythm represents upper A–V nodal rhythm with partial retrograde block which slowly becomes a middle nodal rhythm and that dissociation actually did not occur. Fortunately, however, during the period of synchronization the S–A node again assumed control of the atria (Fig. 3, row 5) and the upright P waves are seen to move out of the QRS complexes as the A–V dissociation ceases. Since the P waves are upright, retro-

grade conduction to the atria is certainly not taking place. Of these three explanations the second is probably more nearly true. These observations in several patients have strengthened our belief in the validity of the term "passive atrial rhythm" for those patients who have retrograde conduction of the atria as evidenced by a negative P wave in leads II and III, but in whom the P–R interval is greater than .10 sec. A–V dissociation induced by atropine provided a valuable clue in differentiating nodal rhythm from lower atrial rhythm.

A–V DISSOCIATION AND THE W–P–W SYNDROME. A–V dissociation with interference after atropine has also been seen in patients with the Wolff-Parkinson-White syndrome. Atropine has been of special interest in these patients for a long time as a means of producing normal conduction. Many authors have commented on the frequency with which normalization occurs following atropine (Duthie[2], Goldman, Crosby

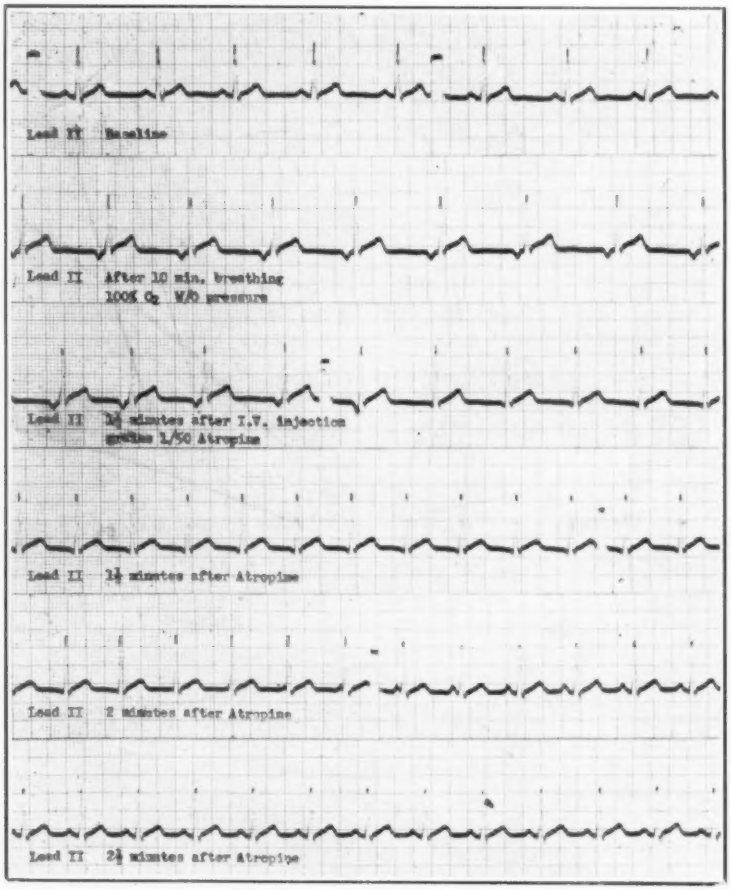
Lead II Baseline
Lead II After 10 min. breathing
100% O2 W/O pressure
Lead II 1½ minutes after I.V. injection
grains 1/50 Atropine
Lead II 1½ minutes after Atropine
Lead II 2 minutes after Atropine
Lead II 2½ minutes after Atropine

Fig. 3.—A–V dissociation with interference in a patient with an atrial rhythm. During the period of synchronization the sinus node reassumes control of the atria.

and Griffith[3], Ohnell[13]). It is probably fair to state that atropine will produce a more normal appearing electrocardiogram in some cases of the Wolff-Parkinson-White syndrome but not in others.

Electrocardiograms from the same patient are depicted in Figs. 4 and 5. The early effects of atropine sulfate lead electrocardiogram was recorded (Fig. 5). Shortly after the atropine injection a definite change occurred and the P waves in leads II and III became inverted along with an increased abnormality of the QRS complexes. The QRS duration increased from .11 sec. to .14 sec. The development of inverted P waves pointed to

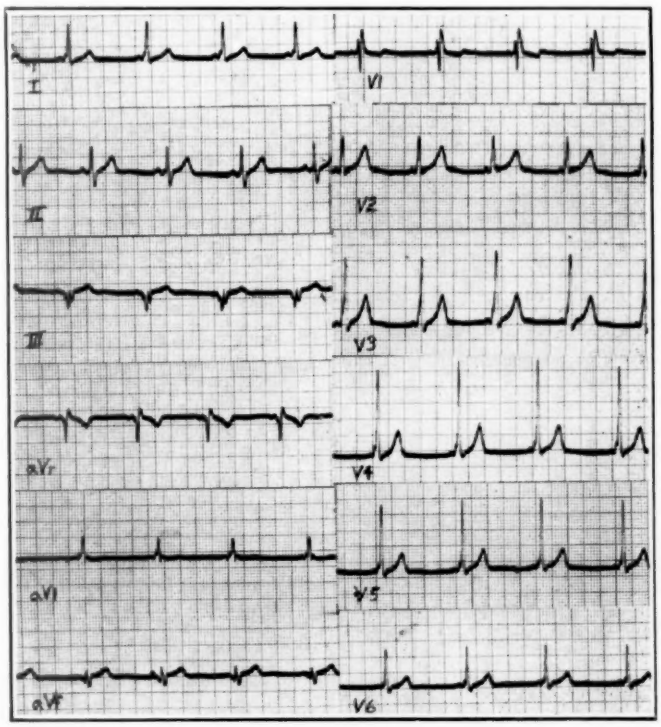

Fig. 4.—Typical tracing in the Wolff-Parkinson-White syndrome P–R interval .10 sec., QRS duration .12 sec.

produced interesting changes in his electrocardiogram and may prove to be of importance in the better understanding of this conduction defect. The patient's usual electrocardiogram is seen in Fig. 4 and shows the typical Wolff-Parkinson-White syndrome. He was given 0.8 mg. atropine sulfate intravenously and a simultaneous 3 a "passive atrial rhythm" (which has been seen to follow atropine in a number of patients) or to an upper nodal rhythm. A–V dissociation with interference then occurred which points to this being an atrial rhythm as was described in the previous case (Fig. 3). With the onset of A–V dissociation the ventricles came under control of the

A–V node and definite normal QRS complexes were seen. Thus impulses originating in the A–V node were conducted normally to the ventricular muscle mass. The pacemaker for the atria was an ectopic one.

The increased abnormality of the QRS complexes prior to A–V dissociation may mean that this ectopic atrial focus was in closer proximity to the accessory pathway. With the onset of A–V dissociation, however, the pacemaker for the atria and the A–V node controlling the ventricles discharged at approximately the same time. Impulses from the A–V node thus activated the ventricles before impulses from above the A–V node could reach any area of the ventricular wall via the bundle of Kent, via diseased portions of the A–V node, or by any other short circuit which these impulses are thought to take. In our experience normal ventricular conduction has always been present in patients with the Wolff-Parkinson-White syndrome when the ventricles are under control of the A–V node. It has become apparent from these studies that the changes in the electrocardiogram during the early stages of atropine activity may prove to be of much value and interest in studying the Wolff-Parkinson-White syndrome.

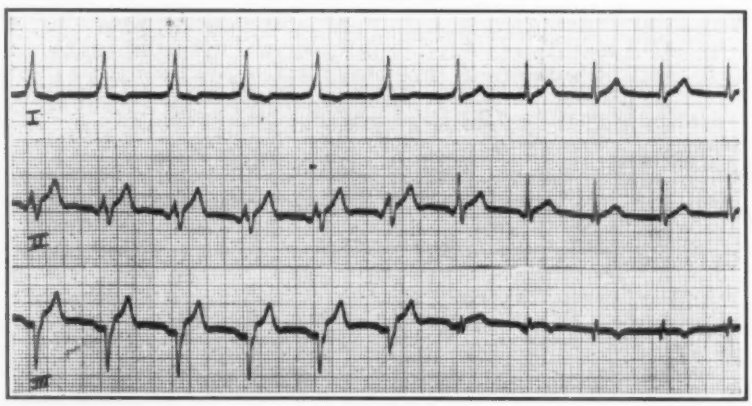

Fig. 5.—Leads I, II, and III from same patient as in Fig. 5 shortly following intravenous atropine sulfate. An ectopic atrial focus is present and there is increased abnormality noted in the QRS complexes. A–V dissociation occurs and normalization of the QRS complexes is seen.

A–V DISSOCIATION AND VENTRICULAR PARASYSTOLE. Interesting observations are possible in certain conduction defects and arrhythmias when A–V dissociation occurs after the intravenous administration of atropine. The tracing from a patient with a parasystolic ventricular focus is shown in Fig. 6. In this short strip, and in other recordings, marked variations in the P–R interval and in the configuration of the QRS complexes were apparent. A parasystolic focus is an ectopic pacemaker which may be atrial or ventricular in origin. The ectopic focus has a basic rhythmicity of impulse formation and is capable of assuming the role of cardiac pacemaker should the normal pacemaker of the heart cease functioning or slow beyond a certain critical rate. The parasystolic focus appears to be "protected" in that it is not excited to discharge by stimulation from the surrounding muscle mass. Thus it is

able to continue its rhythmic discharge and is capable of exciting the heart muscle while the surrounding heart muscle is not in a refractory state. If the heart muscle is excited only by the normal sinus pacemaker a normal configuration of the P–QRS–T complex is seen. If the heart muscle is excited primarily by the ventricular parasystolic focus the P–QRS–T complex will appear as a typical premature ventricular contraction. When the heart muscle is excited by impulses from the supraventricular focus and also from the ectopic parasystolic ventricular focus the complexes will have

of having three active pacemakers for the heart. The atria were stimulated by the sinus node and for 10 beats the ventricles were stimulated alternately from the focus in the A–V node and from the parasystolic focus. Ventricular capture by the atria then occurred and the last three beats were sinus in origin.

During the period of A–V dissociation the atria and the ventricles (when the latter are under control of the A–V node) have equal rates and are synchronous. The parasystolic ventricular focus produces ventricular prematurities. That prematurities do not alter

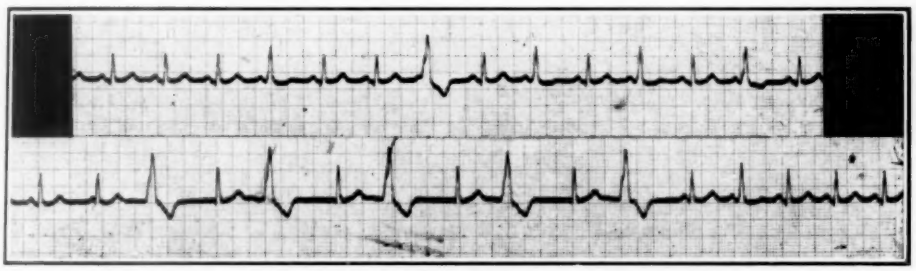

Fig. 6.—Parasystole with A–V dissociation following intravenous atropine sulfate. P waves are seen in the descending stroke of the T waves in the premature complexes.

configurations somewhere between the normal and the premature ventricular complexes. These are commonly called "fusion beats" and their form depends upon the extent to which each of the pacemakers contribute to ventricular excitation. Pick[14] has precisely defined parasystole of both atrial and ventricular ectopic origin.

In Fig. 6 (upper) the first 3 beats are sinus in origin, the 4th, 9th, 11th and 13th are fusion beats. The 7th beat appears as a typical premature ventricular contraction. The lower strip was taken shortly after the intravenous administration of 1.2 mg., atropine sulfate. A–V dissociation occurred with the onset of the second P wave, resulting in the interesting phenomenon

the rhythmic firing of the S–A node and the A–V node is evident from inspection of the record; while the ventricles are stimulated by the A–V node the P wave of atrial excitation is lost in the QRS complex. When the parasystolic focus causes a premature ventricular contraction the P wave of atrial excitation is seen in the descending limb of the T wave. Since the S–A node and the A–V node are discharging at essentially the same rate we can assume the A–V node discharges at the time we see the P wave even though the ventricles are under control of the parasystolic focus. The next QRS complex of A–V nodal origin again obscures the P wave which would fall at precisely the same time.

Since this occurs it is quite certain that neither the S–A node or the A–V node are excited by the ventricular prematurity and they continue to discharge without a change in rate or rhythm.

INDUCED ATRIAL RHYTHM. In addition to A–V dissociation, other transitory effects of atropinization occur. During the very early action of atropine the cardiac pacemaker may change from the sinus node to an atrial focus. Although not as commonly seen as A–V dissociation, it occurs often enough to be mentioned. In Fig. 7 leads V_2, I, II and III were simultaneously recorded 25 seconds after the intravenous injection of 0.8 mg. atropine sulfate. The changes are best seen in lead II. The first 3 P waves are sinus in origin and are essentially alike. The 4th complex probably represents an atrial fusion beat with both the sinus node and an ectopic focus in the atria initiating atrial excitation, although one cannot exclude wandering of the pacemaker. The last 5 P waves result from an ectopic atrial pacemaker. In this particular case the ectopic focus continued as the cardiac pacemaker after the atropine had reached its maximum effect. In other instances, however, the sinus node may assume control as the atropine exerts its full anticholinergic action.

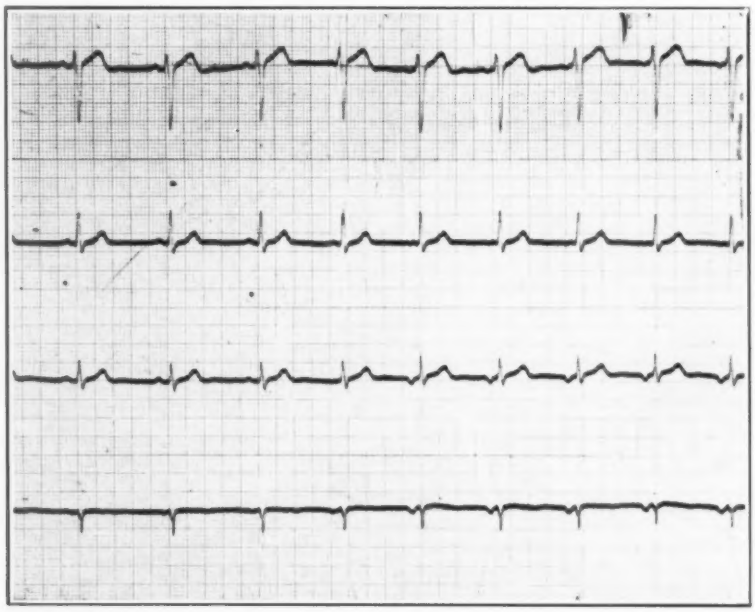

Fig. 7.—Development of an atrial rhythm following intravenous atropine sulfate.

INDUCED A–V BLOCK. Changes in conduction across the A–V junction may also appear in association with A–V dissociation or when there is a change in the cardiac pacemaker from the sinus node to an atrial focus. A series of tracings from a patient in whom a continuous electrocardiogram was run after the intravenous administration of 0.8 mg. atropine sulfate is seen in Fig. 8. The first strip shows an initial sinus bradycardia and in the last complex

A–V dissociation with interference occurs. This is followed by a short period of transitory synchronization. After synchronization the P waves can be seen distorting the T waves to various degrees. In the fourth strip apparent ventricular capture occurs. An interesting phenomenon then takes place which has been seen in several different patients. The P–R interval becomes gradually more and more prolonged until the impulse fails to stimulate the ventricles and 2° A–V block occurs. The seventh atrial complex in the fifth strip occurs during the refractory phase of the A–V junction and is blocked. The pattern is repeated several times. The abnormalities in conduction were seen for approximately 70 sec., and then disappeared as atropine produced its full anticholinergic effect.

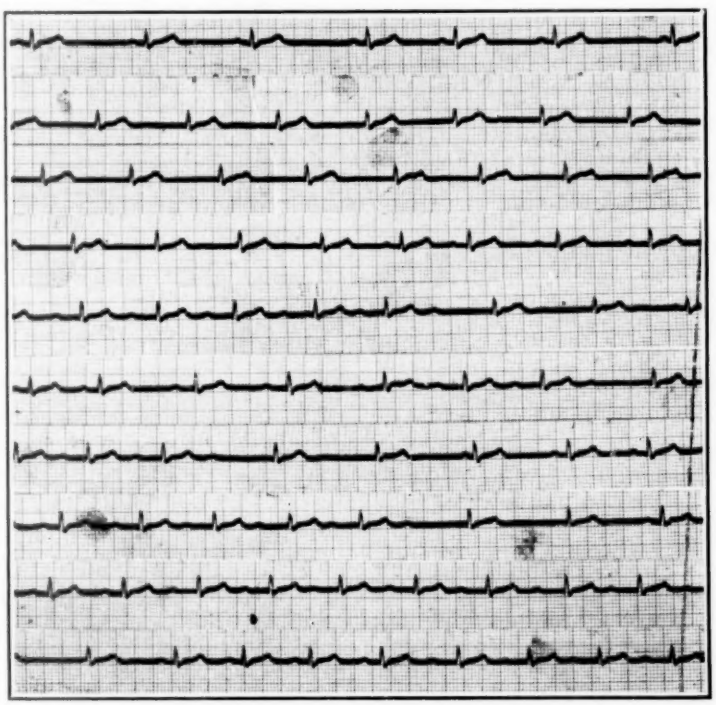

Fig. 8.—A–V dissociation with interference followed by 2° A–V block. See text.

Atropine induced atrial rhythm and 2° A–V block is seen in Fig. 9, 30 seconds following the intravenous administration of 1.2 mg. atropine sulfate. Prior to atropine a pronounced bradycardia was evident and was associated with a changing pacemaker. Simultaneous leads gave evidence that, during the bradycardia, the cardiac pacemaker was shifting in the sinus node itself, although the possibility of a shift into the atria cannot be absolutely excluded. In Fig. 9 (top strip) P waves of different form are seen. Thirty seconds following the atropine atrial rhythm developed (second strip) associated with varying degrees of A–V block. Two distinct periods of the

Wenckebach phenomenon were produced. In the second strip the 4th P wave is from an entirely new focus in the atria and is premature. The cardiac rate increases suddenly from 40 per minute to approximately 90 per minute. The P–R interval increases for 3 cycles and then at least one, and probably two, consecutive atrial impulses are blocked. The asystolic period is terminated by a nodal escape beat. This sequence is repeated before an undisturbed atrial rhythm is established. Over the next 40 seconds the P–R interval decreased slowly from .20 sec. to a final .10 sec. (bottom strip). Three minutes later a normal sinus rhythm appeared.

In this patient a wandering of the cardiac pacemaker was evident prior to the atropine injection. Atropine seemingly precipitated yet another supranodal focus to assume the role of cardiac pacemaker. The sudden doubling of the cardiac rate associated with the activation of the new focus may account for the transient disturbance in conduction across the A–V node. With an increased heart rate the relative refractory period of cardiac tissue is increased.

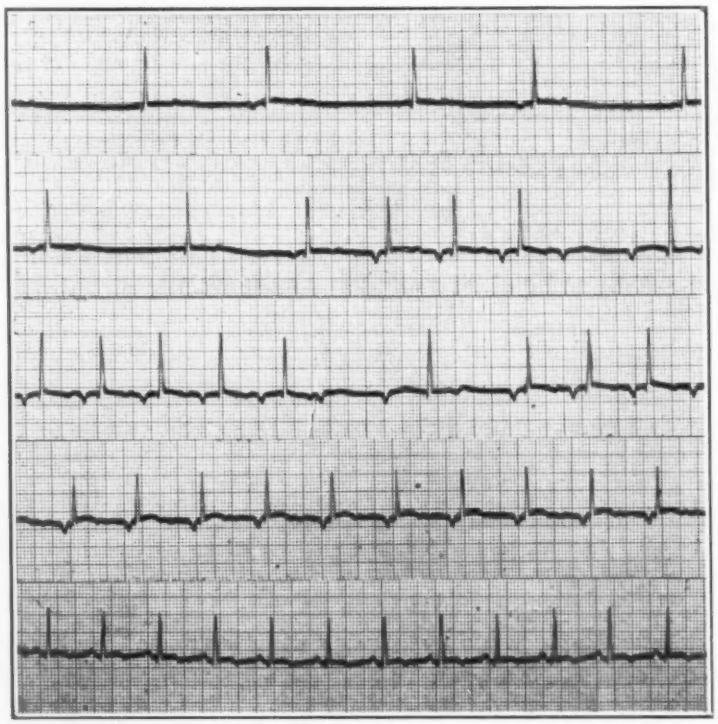

Fig. 9.—Ectopic atrial pacemaker and 2° A–V block initiated by atropine sulfate given intravenously.

ATROPINE AND OTHER DRUGS. Atropine in certain instances is not a completely innocuous drug as shown by Jacobson and Adelman[6]. They studied patients who were under cyclopropane anes-

thesia for various surgical procedures. Some of the patients were also curarized. They were interested in studying the effects of the intravenous administration of neostigmine and atropine in these patients since several instances of immediate cardiovascular collapse and death had been noted to follow this combination. The patients while under anesthesia were given 0.5 mg. to 2.0 mg. neostigmine. Continuous electrocardiographic monitoring was done. After the full cholinergic action of the neostigmine became apparent (with bradycardia, profound disturbance of atrioventricular conduction, marked depression of the sinus node and instances of sinus arrest), 0.8 mg. atropine sulfate was given intravenously. The responses were striking. In most of the patients various degrees of increased ventricular irritability occurred as shown by ventricular premature contractions, ventricular tachycardia, (of multifocal origin) and in one instance ventricular flutter.

Jacobson and Adelman felt that the atropine had successfully blocked the muscarinic action of neostigmine but did not block the nicotinic effect. The combination produced the same effects as would be produced by the administration of an adrenergic drug to a patient with increased cardiac irritability. The adrenergic effect of the unopposed nicotinic action of the neostigmine would be even more likely to produce marked cardiac irritability in the face of cyclopropane anesthesia. The selective action of atropine may be of importance in these patients. The atropine was given during a period of intense cholinergic stimulation. This would tend to increase the early phase of partial atropinization.

It has been shown that atropine may induce ectopic foci to assume the role of cardiac pacemaker, but in our experience no ventricular focus was seen to develop in a large number of patients. However, if the vagotonic influences on the supraventricular areas is intense enough (as after neostigmine) the early release of a ventricular focus from vagal control by the atropine may precipitate transient idioventricular rhythms.

Summary. 1. Atropine sulfate is a potent cardiac parasympatholytic blocking agent.

2. There are three distinct phases of atropine action on the heart. These include an initial vagotonic effect, a transient period of vagal imbalance at different levels of the conduction system, and a final prolonged period of parasympathetic blockage.

3. The changes seen during the early action of atropine are similar to those seen when vagal imbalance is produced by various simple respiratory procedures.

4. Use may be made of this early action of atropine in the investigation of certain arrhythmias and conduction defects.

5. Although the cardiac actions of atropine in the usual clinical doses are benign, when combined with actions of drugs, such as neostigmine, serious arrhythmias and conduction defects may occur.

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(Interlingua on page 286)

SUMMARIO IN INTERLINGUA

(See page 277 for original article)

Effectos De Repetite Morsuras De Serpentes Venenose In Humanos

1. Le effectos de repetite morsuras de serpentes venenose esseva studiate in 14 patientes. Un patiente habeva 12 morsuras differente de serpentes venenose, un altere habeva 10, 2 habeva 6, un habeva 5, 3 habeva 4, un habeva 3, e 5 habeva 2. Con 3 exceptiones, omne le serpentes que habeva infligite le morsuras esseva crotalidas nord-american.

2. Cinque del patientes habeva permanente defectos local, como per exemplo atrophia muscular e amputationes digital, in consequentia del morsuras de serpente. Esseva notate nulle caso de chronic morbo hepatic o renal.

3.Nulle constatationes clinic o laboratorial indicava que iste patientes habeva disveloppate permanente immunitate a veneno crotalidal. Le absentia de immunitate permanente esseva attribuite primarimente al prolongate e irregular intervallos inter le invenenationes e al curte periodo latente inter un morsura e le disveloppamento de invenenation clinic que non provide satis tempore pro le disveloppamento de un effecto reinfortiatori super le production de anticorpore. Altere possibile factores contributori es le facto que le morsuras esseva infligite per differente species, le inhibition antiveninic de immunitate active, e le variation del doses de veneno injicite.

4. Dece-tres del 14 patientes con repetite invenenationes esseva subjicite a tests de grattage pro allergia contra veneno de serpentes. Esseva trovate que 4 esseva allergic contra veneno de crotalo o de ancistrodon o de ambes. Plure patientes exhibiva allergia contra le veneno de serpentes zoologicamente relationale con le specie que habeva mordite les. Per exemplo, il es possibile que un patiente deveni allergic contra veneno de ancistrodon ben que ille esseva previemente mordite per crotalos. Le severitate de repetite morsuras de serpente in patientes non-allergic depende del characteristicas del invenenation individual e non de effectos cumulative de previe morsuras de serpente.

OBSERVATIONS ON THE VARIATION OF TOTAL SERUM CHOLESTEROL LEVELS IN NORMAL INDIVIDUALS AND IN PATIENTS WITH CORONARY HEART DISEASE

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Many investigators (Gertler and White[2], Katz *et al.*[3], Lawry *et al.*[4], Man and Gildea[5], Page *et al.*[6], Sperry[7,8], Technical Group[9], Thomas and Eisenberg[10]), employing different assay procedures have noted that the normal variability of serum cholesterol levels in individual human subjects may be considerable.

While there is a wide divergence of opinion as to the role cholesterol plays in atherosclerosis, the physician seeking to employ dietary regimens and other agents for reducing blood cholesterol is faced with the additional problem of establishing the patient's "normal" serum cholesterol level. The latter is necessary if he is to judge whether the treatment used is effecting a significant lowering of cholesterol levels within the limits of this "normal" variability.

This study was undertaken with the hope of uncovering some guides to be employed in the estimation of "normal" variability when therapy is planned.

Procedure. Two groups were used in this study. One, designated Control, was composed of 10 normal men; the other, designated Hospital was made up of 14 patients with recent acute myocardial infarction on Dicoumarol therapy. Total serum cholesterol measurements were performed by the procedure of Abell *et al.*[1].* The diets of the Control group were unrestricted, while the Hospital group received the regular hospital diet.

The data obtained from these groups could be examined for variability in two ways. One, a direct measure of variation in terms of mg. per 100 ml. total serum cholesterol is shown as Fig. 1. Figure 2 refers to the percentage of the individual mean value to which the most widely divergent determination amounted.

Other pertinent data as to age, technical error, and number of determinations performed are shown in Table 1.

Interpretation. From Fig. 1 it is seen that the values obtained from individuals may vary widely. Roughly equivalent spreads being obtained from both the Control and Hospital groups, it would appear that this variation is not a function of the clinical condition, or indeed of the diet, since no attempt

*Performed by the Department of Pharmacology, Warner-Lambert Research Institute, Morris Plains, New Jersey.

was made to control the diets of the Control group, while the Hospital group were under some measure of control. The arbitrary decile divisions reveal that in both groups the determinations fell within 40 mg. per 100 ml. of the mean approximately 90% of the time, and within 30 mg. per 100 ml. of the mean approximately 75% of the time. The remaining 10% of the determinations falling outside the 40 mg. per 100 ml. decile may not be disregarded since 30% of the Control patients and 44% of the Hospital patients exhibited variations of this magnitude at one time or another. Correction for technical error of measurement is not allowable since it must be considered equally likely for it to vary positively as negatively.

From inspection of Fig. 2 it is apparent that the per cent variation of the most deviant determination against the mean is equally variable, individuals of the Control group exhibiting variations amounting to from 6 to 27% and the Hospital group varying from 3 to 29%.

From these data, an attempt was made to determine if the total serum

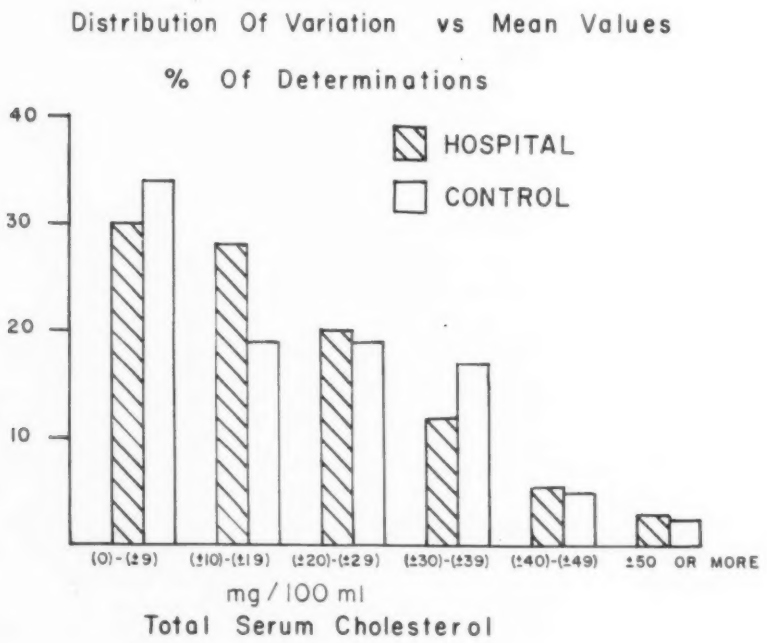

Fig. 1.

TABLE 1.—PERTINENT DATA CONCERNING CONTROL AND HOSPITAL GROUPS.

Group	*No. of Determinations (average)*	*Age (average)*	*Total Serum Cholesterol mg./100 ml.*	*Standard Error of Mean*	*S.D.*
Control	4	43 yrs.	226	± 12.8	29.2
Hospital	10	53 yrs.	266	± 7.1	44.6

cholesterol levels of the Control group differed significantly from those of the Hospital group. Employing a "t" test, this was found to be true, with $p = .05$. The age variable is thought to be insignificant since the Technical Group[9] found the age variable in large samples to be less than 4 mg. per 100 ml. total serum cholesterol, and since the data of Wheeler[11] indicate that the normals of the limitations imposed by this variability must be taken into consideration. A minimum of 4 or 5 determinations done on the same day of the week (to minimize dietary variations, if any) should be sufficient to indicate the patient's range of variability. Once this variation is established more accurate judgments as to the efficacy of treatment may be made.

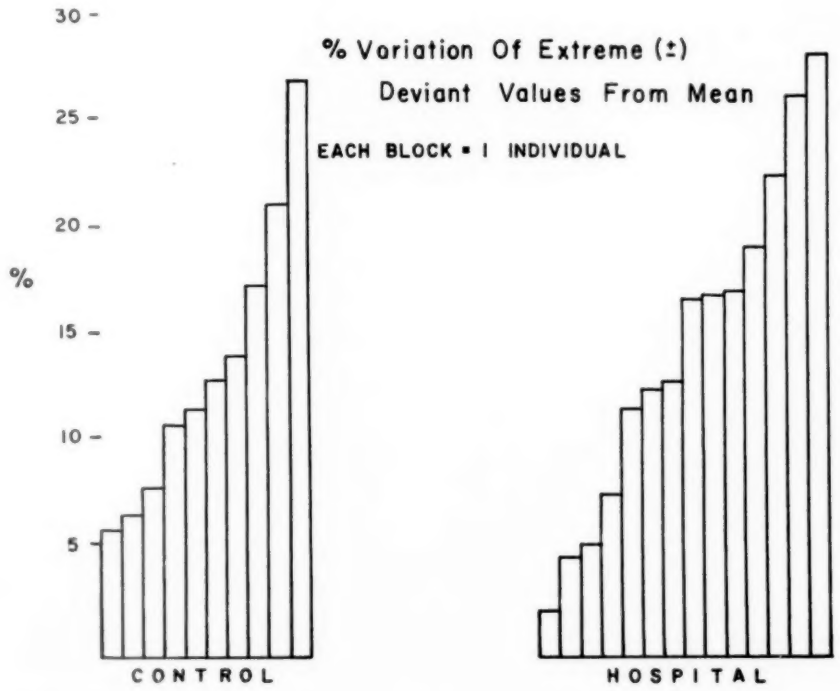

Fig. 2

the Control group show almost the same cholesterol levels as the comparable age group he tested, while the Hospital group is elevated above the levels found by Wheeler[11] for their age group.

Conclusions and Summary. Total serum cholesterol measurements may vary widely in any given individual. The use of such measurements is thought to be of some value in the treatment of hypercholesteremia, but

Based on these data, depressions of more than 20% of the mean pretreatment values (up to 400 mg. per 100 ml. of blood) or of more than 50 mg. per 100 ml. total serum cholesterol may be taken to indicate successful depression of the serum cholesterol if the depressed levels continue. The above may not apply to cases of marked hypercholesteremia since no cases of this type are encountered in this series.

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SUMMARIO IN INTERLINGUA

Observationes Relative Al Variation Del Nivellos De Cholesterol Total In Subjectos Normal E In Patientes Con Morbo Cardiac Coronari

Le nivello del cholesterol total del sero pote variar grandemente in un individuo particular. Le determination del nivello de cholesterol total in le sero es considerate como utile in le tractamento de hypercholesterolemia, sed le limitationes imponite per le variabilitate de ille nivello debe esser prendite in consideration. Un minimo de 4 o 5 determinationes, effectuate le mesme die del septimana (pro reducer le variationes dietari, si tales existe) suffice probabilemente pro indicar le variabilitate que es characteristic del patiente. Post que iste variabilitate es establite, plus accurate conclusiones relative al efficacia del tractamento pote esser tirate.

In consideration de iste factos, depressiones amontante a plus que 20% del valores pretherapeutic medie (usque a 400 mg per 100 ml de sanguine) o a plus que 50 mg per 100 ml de cholesterol total del sero pote esser interpretate como representante successo in le depression del cholesterol del sero, providite que le nivellos deprimite persiste. Iste cifras es forsan non applicabile a casos de hypercholesterolemia de grados marcate, proque nulle tal casos esseva representate in iste serie.

TRANSAMINASES IN SERUM AND LIVER CORRELATED WITH LIVER CELL NECROSIS IN NEEDLE ASPIRATION BIOPSIES

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The glutamic-oxaloacetic (Wroblewski and LaDue[20]) and glutamic-pyruvic (Wroblewski and LaDue[22]) transaminating enzymes are found in increased amounts in the serum of patients with viral hepatitis and other forms of liver disease. It has been noted that the sicker the patient with viral hepatitis, the higher is the peak transaminase activity of the plasma, and that the clinical course of patients is reflected in serial SGOT alterations (Wroblewski, Jervis and LaDue[19]). Patients with decompensated Laennec cirrhosis had higher serum glutamic-oxaloacetic transaminase levels than those with compensated cirrhosis (Molander, Sheppard and Payne[11]), and improvement in liver histology in such patients has been found to correlate with decreases in serum levels of both glutamic-oxaloacetic and glutamic-pyruvic transaminases (Zinke and Leevy[24]).

Destruction of liver cells, with release of intracellular enzyme content into the plasma, has been proposed to account for these increases, although variations in the release, destruction or excretion of the two enzymes may be important contributory mechanisms (Wroblewski and LaDue[21]). In 20 patients with jaundice of varying etiology, the degree of elevation of serum glutamic-oxaloacetic transaminase seemed related to the amount of cellular necrosis observed by microscopic study of liver biopsy specimens (Merrill *et al.*[9]). In a study of serum enzymes of patients with carcinoma in liver, analysis of the results suggested that while lactic dehydrogenase rises reflected the mass of tumor, glutamic-oxaloacetic transaminase elevations reflected necrosis of tissue invaded by metastases (West and Zimmerman[17]). It is thus possible that a laboratory estimation of the serum is available which provides a measure of actual necrosis of parenchymal cells of the diseased liver.

In mice infected with hepatitis virus, the increases in serum transaminases have been shown to be roughly proportional to the degree of liver necrosis (DeRitis, Coltorti and Giusti[5], Friend, Wroblewski and LaDue[6]) as well as to losses of analogous transaminase activities in the livers of the same ani-

mals (DeRitis, Coltorti and Giusti[5]). The glycolytic enzymes aldolase and phosphohexoseisomerase were found to undergo similar redistribution from liver to serum in carbon tetrachloride poisoned mice (Bruns and Neuhaus[3]). In similarly poisoned mice, a correlation was found to exist between the carbon tetrachloride dosage, the extent of liver necrosis produced by it, and the height and duration of increase in serum glutamic-oxaloacetic transaminase (Molander, Wroblewski and LaDue[12]).

Whether the rise in serum transaminases in liver injury is due entirely to redistribution from dying liver cells to serum has been questioned. Failure to detect decrease in glutamic-oxaloacetic transaminase content of hepatic tissue in the presence of marked serum elevations experimentally produced by carbon tetrachloride injury to the liver has been reported (Molander and Friedman[10]). The same observation has been made in regard to hepatic tissue glutamic-oxaloacetic and glutamic-pyruvic transaminases during the course of experimental virus hepatitis in mice at the time these enzyme activities were elevated in the serum (Wroblewski[18]).

Necrosis in the liver is rarely in the form of infarction, being rather a diffusely distributed accumulation of localized necroses among persisting undying cells (Popper and Schaffner[14]). Nevertheless, the process is ordinarily sufficiently diffuse to allow estimation of its degree by study of representative sections of the liver (Waldstein and Szanto[16]). We have attempted, therefore, in a series of 143 needle aspiration biopsies of the liver, taken from 108 patients with real or suspected liver disease, to estimate the extent of necrosis of liver cells by histologic criteria (Popper and Schaffner[14]) for comparison with serum transaminase values determined on the morning of biopsy. In 25 instances, additional liver tissue was obtained (by a second needle insertion and aspiration at the same site and at the same time) for estimation of tissue transaminase activities. Initially, only the glutamic-oxaloacetic transaminase activity was determined in serum and tissue, but both transaminases were estimated in the later patients.

Materials and Method. Transaminase values were determined spectrophotometrically, according the methods of Karmen[8] and Wroblewski and LaDue[21]. For tissue determinations, each biopsy specimen was placed immediately into a tared and cooled weighing bottle previously buried in a beaker containing freezing mixture. Weight was obtained by difference, using an electric microbalance, requiring less than 2 minutes for weighing. The specimens averaged 50 mg. in weight. With the aid of a buffer solution at pH 7.4, the tissue was transferred into a micro-homogenizer and thoroughly disintegrated, then transferred into a 10 ml. volumetric flask and the volume made up to 10 ml. with additional buffer solution. After centrifuging, 0.2 ml. of the supernatant solution thus obtained was used for each of the transaminase determinations according to the methods employed for serum. Units recorded in the tables are those of Karmen, Wroblewski and LaDue, as determined per ml. of serum or per mg. of biopsied liver tissue.

All liver biopsies were obtained with the Roth-Turkel needle, using an intercostal approach except in those patients whose enlarged livers presented in the epigastrium sufficiently to allow the anterior approach. Hematoxylin and eosin stained histologic sections of the biopsied specimens of all patients of this series were collected and examined specifically for the purpose of this study, without reference to recorded transaminase determinations. Specimens of inadequate size were discarded. Evidences of active liver cell necrosis were sought, without reference to etiology or the nature of associated disease. After repeated examinations and comparisons, the sections were divided into 4 groups, representing those considered within normal limits (group 0), showing mild (group 1), moderate (group 2), or severe (group 3) diffuse necrosis. Examples of these are shown in Figs. 1–4.

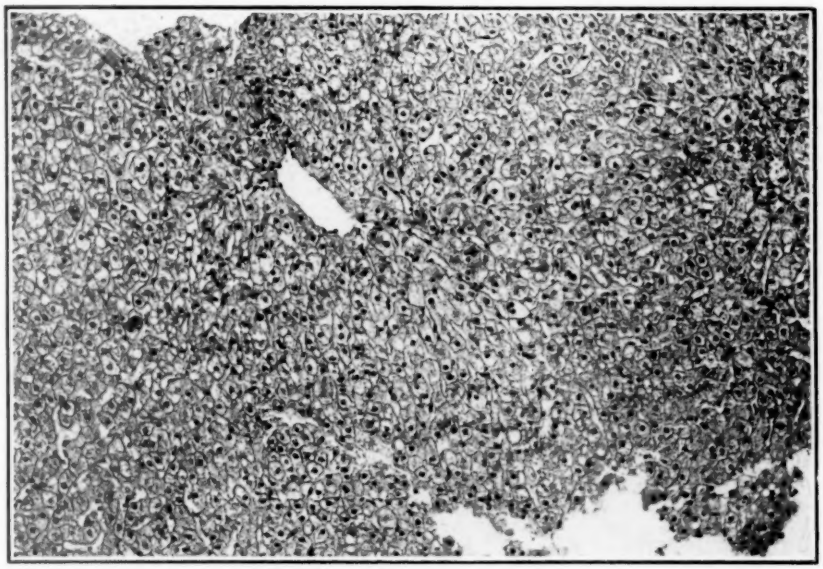

Fig. 1.—Example of histologic grading of liver cell necrosis, grade 0. An entire liver lobule is seen, with central vein at upper left and portal area at extreme upper right. No liver cell necrosis is seen. From a patient recently recovered from viral hepatitis, whose earlier biopsy is seen in Fig. 4. Serum G–O transaminase was 29 units, and G–P transaminase 13 units, on the day of biopsy. Hematoxylin and eosin, × 100.

Fig. 2.—Example of histologic grading of liver cell necrosis, grade 1. Hemochromatosis, showing spotty liver cell degeneration and necrosis in the islands of liver cell parenchyma surrounded by fibrous tissue. Serum G–O transaminase was 59 units, and G–P transaminase 70 units, on the day of biopsy. Hematoxylin and eosin, × 100.

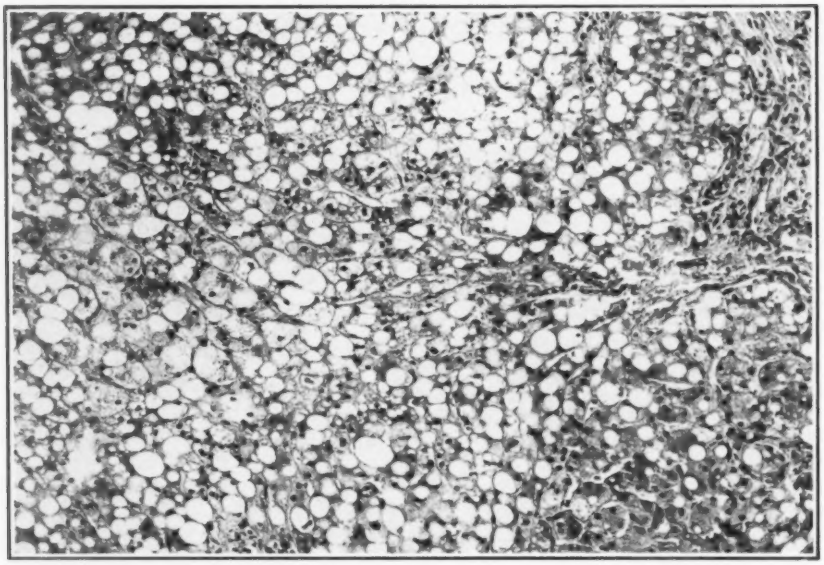

Fig. 3.—Example of histologic grading of liver cell necrosis, grade 2. Fatty septal cirrhosis, showing diffuse inflammatory and lytic necrosis of fatty liver cells. Serum G–O transaminase was 180 units, and G–P transaminase 110 units, on the day of biopsy. Hematoxylin and esosin, × 100.

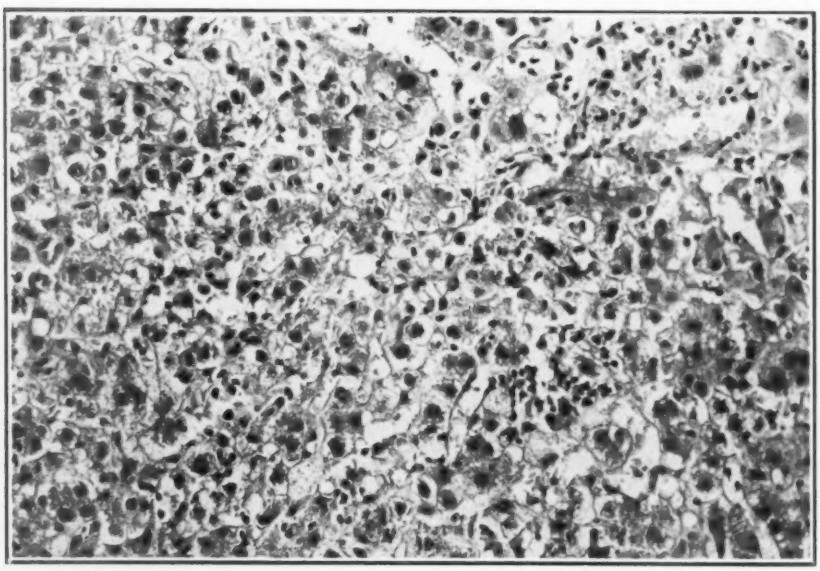

Fig. 4.—Example of histologic grading of liver cell necrosis, grade 3. Acute viral hepatitis, showing widespread coagulative and some inflammatory necrosis of liver cells throughout the lobule. Serum G–O transaminase was 265 units, and G–P transaminase 211 units, on the day of biopsy. Hematoxylin and eosin, × 200.

There were 143 biopsies in the series, obtained from 108 patients. Twenty patients were twice represented in the series, 2 were represented 3 times, 2 patients 4 times, and one patient 6 times. Each biopsy specimen was separately considered for the purpose of this study, and transaminase studies performed on each occasion of rebiopsy. The histologic diagnoses of these biopsies were:

	Biopsies
Normal liver	6
Nonspecific reactive hepatitis	9
Fatty liver	23
Fatty septal cirrhosis	30
Florid cirrhosis	2
Septal cirrhosis	14
Hemochromatosis	2
Biliary cirrhosis	1
Viral hepatitis	10
Cholangiolitic hepatitis	5
Infectious mononucleosis	1
Toxic hepatitis	6
Allergic cholangiolitis (chlorpromazine)	11
Chronic pericholangitis	5
Portal fibrosis	2
Extrahepatic biliary obstruction	5
Hemosiderosis	1
Granuloma	5
Tumor	5

HISTOLOGIC CRITERIA. Our sections were cut at 8 microns thickness. The liver cells generally measured between 20 and 30 microns in diameter, with nuclear diameters up to 10 microns. Serial sections were made to find missing nuclei, and these were identified in subsequent sections when missing in the first. Therefore, anuclear cells were not considered to be necrotic, unless cytoplasmic evidences of necrosis were also present, such as eosinophilic shrinking or hyalinization, ballooning, or loss of cell borders. Nuclear lysis, pyknosis, and fragmentation were identified with necrosis, while nuclear ballooning was tolerated as a reversible degeneration (Baird and Fisher[2]).

Lipofuscin-filled Kupffer cells were considered indicative of recent but not necessarily current liver cell necrosis. Small focal accumulations of phagocytes disrupting hepatic laminae were taken to indicate liver cell destruction at those sites (Fig. 5). Larger foci of necrosis (Figs. 8, 9), and the diffuse necrosis of acute hepatic failure of the chronic alcoholic (Phillips and Davidson[13], Popper, Szanto and Parthasarathy[15]) and of acute viral hepatitis (Fig. 4) were easily notable.

Unicellular necroses were found in all biopsy specimens, and considered to represent normal cellular renewal within the liver (Ashworth and Reid[1]). Judgment as to when this exceeded normal limits was arbitrary. Cell counting was not feasible because of variation in different areas, both within the lobule and among lobules. Many of the specimens were from cirrhotic livers, in which some nodules often showed relatively intact hepatic cytoarchitecture while others showed varying degrees of necrosis. An over-all estimate of the entire available section was used for grading of all specimens. Infiltrative lesions were graded by the degree of liver cell death actually occurring because of invasion or compression, rather than by spatial extension of the lesion (Fig. 10).

Results. Serum glutamic-oxaloacetic transaminase values were available for 130 liver biopsies (Table 1). The 4 grades of necrosis showed a progressive increase in mean SGOT. Of 38 biopsies graded within normal limits, none was associated with elevation of SGOT (upper normal limit, 40 units per ml.). Of 70 biopsies in grade 1 (minimal necrosis), 61 (87%) were associated with normal SGOT values; the remaining 9 (13%) ranged up to 94 units per ml. Of 17 biopsies in grade 2 (moderate necrosis), 12 (71%) were associated with high SGOT values, ranging up to 202 units per ml. All of 5 biopsies in grade 3 (severe necrosis) were associated with abnormal SGOT values, ranging from 91 to 265 units per ml., with a mean value of 166 units.

Serum glutamic-pyruvic transaminase values were available for 50 liver biopsies (Table 2). The 4 grades of necrosis showed a progressive increase in mean SGPT. All but one (94%) of 18 biopsies graded within normal limits were associated with normal SGPT values (upper normal limit, 35 units per ml.), the single exception being only 38 units. Of 20 biopsies in grade 1 (minimal necrosis), 12 (60%) were associated with normal SGPT values; the remaining 8 (40%) SGPT values

ranged up to 158 units per ml. Of 11 biopsies in grade 2 (moderate necrosis), 6 (55%) were associated with high SGPT values, ranging up to 111 units per ml. A single biopsy in grade 3 (severe necrosis) was associated with an SGPT value of 211 units.

Tissue glutamic-oxaloacetic transaminase values were available for 25 biopsy specimens (Table 3). With the exception of grade 1 (minimal necrosis), the grades of necrosis showed a progressive decrease in mean tissue GOT values. The 5 biopsies graded within normal limits ranged from 127 to 256 units per mg. wet tissue, with a mean of 184 units; while the 5 biopsies of grades 2 and 3 (moderate and severe necrosis) ranged from 82 to 164 units per mg., with a mean of 108 units.

Fig. 5.—At right center, a dying liver cell has attracted phagocytes; immediately above and to left, another liver cell shows cytoplasmic eosinophilic shrinkage and nuclear pyknosis, and edges toward extrusion into the sinusoid. Hematoxylin and eosin, × 525.

TABLE 1.—GLUTAMIC-OXALOACETIC TRANSAMINASE VALUES IN SERUM OF PATIENTS COMPARED WITH GRADE OF NECROSIS ESTIMATED HISTOLOGICALLY IN LIVER BIOPSY SPECIMENS OBTAINED THE SAME DAY. UNITS OF ACTIVITY ARE PER ML. OF SERUM; THOSE UP TO 40 ARE CONSIDERED NORMAL.

Necrosis in Liver		*Serum G–O Transaminase*				
Grade of Necrosis	*Total Cases*	*0–40*	*41–100*	*101–200*	*201–300*	*Mean*
0	38	38	0	0	0	17
1	70	61	9	0	0	25
2	17	5	7	4	1	77
3	5	0	1	2	2	166

Fig. 6.—Councilman-like body in sinusoid, a necrotic liver cell of hyalinized cytoplasm and fragmenting pyknotic nucleus about to be extruded from the cell body. Hematoxylin and eosin, × 855.

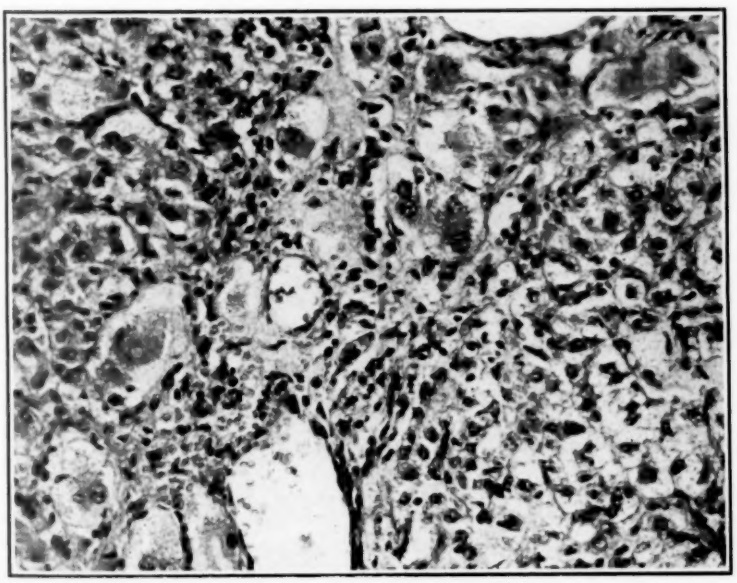

Fig. 7.—Pericentral liver cells showing ballooning and nuclear lysis. From a patient with acute viral hepatitis. Hematoxylin and eosin, × 220.

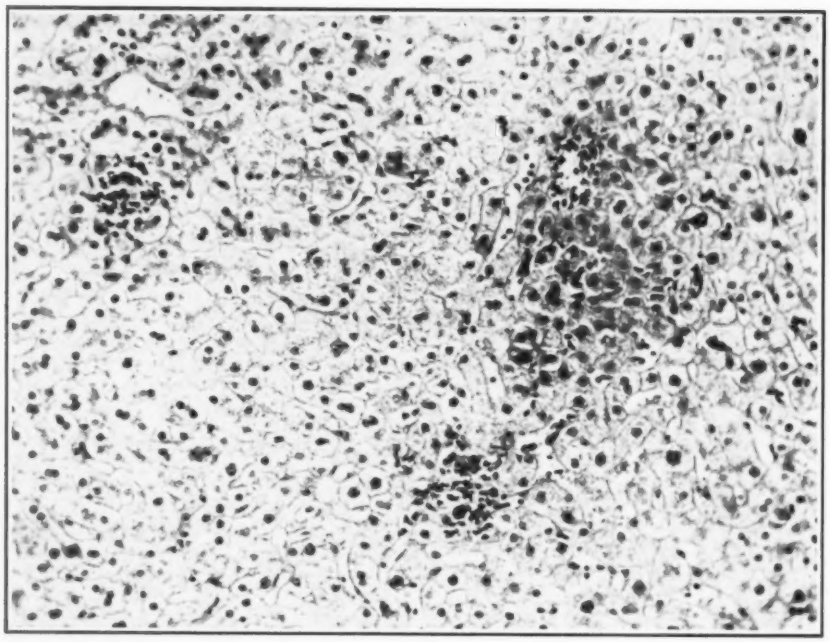

Fig. 8.—One small focal necrosis lies below the central vein at upper left. Two additional focal necroses at right are at opposite ends of a large area of coagulative liver cell degeneration and necrosis. From a patient with chlorpromazine jaundice (Ref. [23], case 3). Hematoxylin and eosin, × 170.

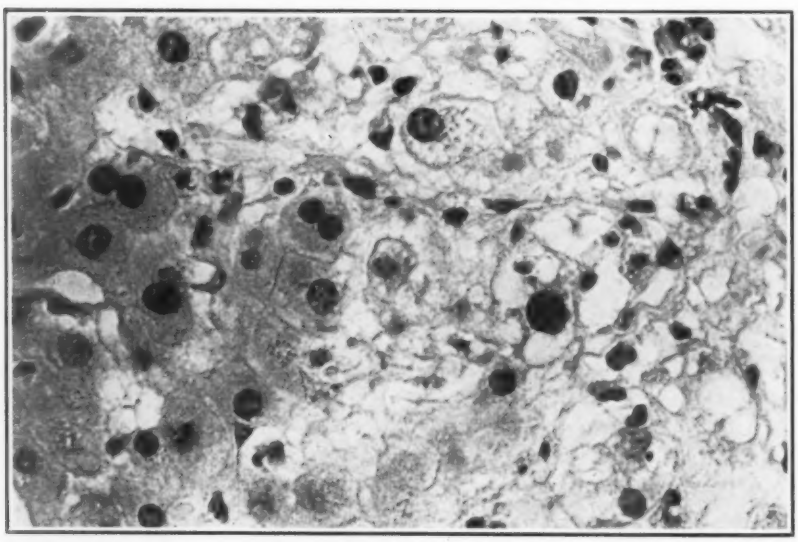

Fig. 9.—Edge of a large area of feathery necrosis. There is a gradual transition from regenerating liver cells at left to complete dissolution with ghost-like residual reticulated networks at right. From a patient with chlorpromazine jaundice (Ref. [23], case 2). Hematoxylin and eosin, × 470.

Fig. 10.—Pericholangitis, with diffuse invasion of periportal lobular zone by inflammatory infiltrate, isolating and destroying portions of liver cell plates. Hematoxylin and eosin, × 240.

TABLE 2.—GLUTAMIC-PYRUVIC TRANSAMINASE VALUES IN SERUM OF PATIENTS COMPARED WITH GRADE OF NECROSIS ESTIMATED HISTOLOGICALLY IN LIVER BIOPSY SPECIMENS OBTAINED THE SAME DAY. UNITS OF ACTIVITY ARE PER ML. OF SERUM; THOSE UP TO 35 ARE CONSIDERED NORMAL.

Necrosis in Liver		*Serum G–P Transaminase*				
Grade of Necrosis	*Total Cases*	*0–35*	*36–100*	*101–200*	*201–300*	*Mean*
0	18	17	1	0	0	19
1	20	12	7	1	0	39
2	11	5	3	3	0	54
3	1	0	0	0	1	211

Tissue glutamic-pyruvic transaminase values were available for 13 biopsy specimens (Table 4). The 4 grades of necrosis showed a progressive decrease in mean tissue GPT values. The 4 biopsies graded within normal limits ranged from 27 to 165 units GPT per mg. wet tissue, with a mean of 74 units; while the 3 biopsies of grades 2 and 3 (moderate and severe necrosis) ranged from 10 to 38 units per mg., with a mean of 25 units.

To determine whether the trauma of needle biopsy of the liver was itself sufficient to cause a rise in serum transaminase, the first 20 patients of the series were additionally examined for serum glutamic-oxaloacetic transaminase activity on the day following biopsy. No significant deviation was found in any patient.

Discussion. The results show good correspondence between the glutamic-oxaloacetic and glutamic-pyruvic trans-

aminase activities of serum and the degree of necrosis histologically estimated in liver biopsies taken the same day. This not only confirms the serum estimation of these transaminases as a fairly reliable index of necrosis in the diseased liver, but also lends confidence to the appraisal of histologic evidences of necrosis in representative liver biopsy specimens obtained by needle aspiration.

proach would have been to relate tissue transaminases to tissue nitrogen content, before attempting correlation with histologic evidences of necrosis. Despite these detracting influences, an inverse correspondence was obtained between tissue transaminase activities and the grade of necrosis in biopsies.

The rise in serum transaminases found in patients with obstructive jaundice, whether extrahepatic or in-

TABLE 3.—GLUTAMIC-OXALOACETIC TRANSAMINASE VALUES IN BIOPSIED LIVER TISSUE OF PATIENTS COMPARED WITH GRADE OF NECROSIS ESTIMATED HISTOLOGICALLY IN A SECOND BIOPSY SPECIMEN OBTAINED AT THE SAME SITE AT THE SAME TIME. UNITS OF ACTIVITY ARE PER MG. OF WET TISSUE.

Necrosis in Liver		*Tissue G–O Transaminase*			
Grade of Necrosis	*Total Cases*	*201–300*	*101–200*	*0–100*	*Mean*
0	5	2	3	0	184
1	15	1	8	6	112
2	3	0	2	1	124
3	2	0	0	2	83

TABLE 4.—GLUTAMIC-PYRUVIC TRANSAMINASE VALUES IN BIOPSIED LIVER TISSUE OF PATIENTS COMPARED WITH GRADE OF NECROSIS ESTIMATED HISTOLOGICALLY IN A SECOND BIOPSY SPECIMEN OBTAINED AT THE SAME SITE AT THE SAME TIME. UNITS OF ACTIVITY ARE PER MG. OF WET TISSUE.

Necrosis in Liver		*Tissue G–P Transaminase*			
Grade of Necrosis	*Total Cases*	*101–200*	*51–100*	*0–50*	*Mean*
0	4	1	1	2	74
1	6	1	1	4	42
2	2	0	0	2	33
3	1	0	0	1	10

The determination of transaminase activities in biopsied liver tissue was subject to additional sources of technical error in handling of the tissue. Transaminase activities were determined per mg. of total liver tissue, taking no account of the varying amounts of fat and fibrous tissue present in many of the specimens; while the degree of necrosis of liver cells bore no direct relation to the amounts of fat or fibrous tissue present. A more accurate ap-

trahepatic, is most probably a reflection of liver cell necrosis. The glutamic-oxaloacetic transaminase activity of human T-tube bile has been found insufficient to provide any major contribution to the serum by regurgitation in obstructive jaundice (Merrill *et al*[9]). Focal necroses quickly develop in the liver after uncomplicated sudden obstruction of the common bile duct, probably because of the cytotoxic effect of bile dammed up within liver cells

(Cameron, Griffiths and Hasan[4]). We have been able to produce feathery necrosis of liver cells by dipping fresh liver biopsy specimens into necropsy bile (Graham and Zelman[7]). The liver biopsies in this series from patients with extrahepatic biliary obstruction all showed necrotic bile-filled liver cells in the central zones of the lobules. Invasion of the limiting plate by a pericholangitic cellular exudate, with destruction by lysis of periportal liver cells (Fig. 10) was also seen in some of these.

Biopsies from patients with intrahepatic cholestasis did not always show centrolobular necroses, but many did, and foci of feathery necrosis occurred in some (Fig. 9). Although case reports of chlorpromazine jaundice (allergic cholangiolitis) have commonly failed to discover necrosis of liver cells in single biopsies, we have studied 9 such patients by serial biopsies and found significant necrosis at some stage in each (Zelman[23]) (Fig. 8). Fairly large necroses occurred occasionally. It may be that mild attacks of allergic cholangiolitis are unaccompanied by liver cell necrosis, but in that event we should expect the serum transaminase levels to be unaffected.

Summary. During a series of 143 aspiration biopsies of the liver obtained from 108 patients, simultaneous determinations were made of serum glutamic-oxaloacetic transaminase 130 times and of serum glutamic-pyruvic transaminase 50 times. An excellent correspondence obtained between the extent of necrosis of liver cells as estimated histologically in biopsy specimens and the rise in serum activity of either transaminase.

An inverse relationship to the degree of necrosis of liver cells was found with 25 tissue glutamic-oxaloacetic and 13 tissue glutamic-pyruvic transaminase activities determined in companion liver biopsy specimens.

The trauma of needle biopsy of the liver failed to affect the serum glutamic-oxaloacetic transaminase activity of 20 patients reexamined the following day.

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SUMMARIO IN INTERLINGUA

Transaminases In Sero E Hepate Correlationate Con Necrose De Cellulas Hepatic In Biopsias De Aspiration Per Agulia

In un serie de 143 biopsias aspirational del hepate in 108 patientes, determinationes simultanee del transaminase glutamic-oxaloacetic del sero esseva facite in 130 occasiones e del transaminase glutamic-pyruvic del sero in 50 occasiones. Un excellente correspondentia esseva trovate inter le grado de necrosis in le cellulas hepatic—estimate histologicamente in specimens bioptic—e le augmento del activitate seral del un e del altere transaminase.

Un relation inverse esseva constatate inter le grado de necrosis in le cellulas hepatic e le activitate histic de transaminase glutamic-oxaloacetic in 25 casos e inter ille grado de necrosis e le activitate histic de transaminase glutamic-pyruvic in 13 casos in que le determinationes esseva effectuate in specimens de biopsia hepatic de origine commun.

Le trauma del biopsia a agulia in le hepate non afficeva le activitate seral de transaminase glutamic-oxaloacetic de 20 patientes qui esseva re-examinate le sequente die.

SUMMARIO IN INTERLINGUA

(See page 341 for original article)

Le Effecto De Therapia Electro-Convulsive Super Le Lipidos Del Sero

1. Le effecto de therapia electro-convulsive super le concentrationes seral de cholesterol, phospholipidos, e lipoproteinas esseva studiate in 14 patientes psychiatric.

2. Nulle significative alteration del nivellos seral de lipido esseva trovate in le majoritate del subjectos, tanto como effecto del expectation del therapia electro-convulsive como etiam como effecto del convulsion mesme.

3. Le constatationes es discutite in relation con le effectos de stress emotional e physiologic super le lipidos del sero.

DETECTION OF INTRAHEPATIC METASTASES BY BLIND NEEDLE LIVER BIOPSY

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Intelligent management of the cancer patient requires a knowledge of the sites and extent of the neoplasm. Blind needle biopsy of the liver is a readily available means for ascertaining the presence of hepatic metastases. By providing a tissue diagnosis needle biopsy not only confirms the clinical impression and enhances the accuracy of prognosis, but it also opens the way for attempts at palliation by surgery (Brunschwig[3,4], Pack and Miller[16], Smith[20]), Roentgen irradiation (Phillips[17]) and chemotherapy (Karnofsky[11]). Our experience with the procedure of blind needle biopsy in patients with intrahepatic metastases indicates that it is highly efficient and is attended by no greater risk than the normal risk of needle biopsy in other accepted indications.

Methods and Materials. Liver biopsy was undertaken 113 times for the purpose of detecting neoplasm of the liver. In each instance metastatic carcinoma was either the primary clinical diagnosis for which confirmation was sought, or it entered into the differential diagnosis.

Patients were screened for latent hemorrhagic tendencies. Bleeding time, clotting time and prothrombin time were determined and platelets were counted. General and local contraindications were observed. The Vim-Silverman liver biopsy needle or the Terry liver biopsy needle was used. In the majority of instances the biopsy was performed transabdominally, and where feasible, an attempt was made to secure tissue directly from a palpable liver nodule.

Results. Malignant neoplasm was found in 76 of 113 patients. Seventy-two (64%) had metastatic neoplasms. Four patients had primary hepatic carcinoma. In Table 1 are listed the histologic diagnoses made in the 76 patients with intrahepatic malignancy. In Table 2 are listed the diagnoses made in patients from whom carcinoma tissue was not obtained.

TABLE 1.—HISTOLOGIC DIAGNOSES IN 76 INTRAHEPATIC NEOPLASMS DETECTED BY NEEDLE BIOPSY

	Number of Cases
Primary hepatic carcinoma (hepatoma)	4
Metastatic carcinoma unclassified	30
Metastatic adenocarcinoma	32
Metastatic anaplastic carcinoma	6
Metastatic neuroblastoma	1
Metastatic myosarcoma	1
Metastatic melanoma	2

TABLE 2.—DIAGNOSES IN 37 PATIENTS FROM WHOM INTRAHEPATIC NEOPLASM WAS NOT OBTAINED

	Number of Cases
Normal liver tissue	23
Fatty metamorphosis	5
Nonspecific reactive hepatitis	3
Intrahepatic cholestasis	1
Foreign-body giant cells	1
Granuloma unspecified	1
Necrotic tissue	1
No liver tissue	2

The site of the primary tumor was known in only 22 of the 113 patients. In 3 patients neoplasm had not been suspected prior to liver biopsy. Ward *et al.*[22] found that among a group of

111 patients proved by one means or another to have malignant neoplasm of the liver, blind needle biopsy revealed the lesion in 82 (74%). Sixty-six (60%) were metastatic liver lesions. Bowden and Kravitz[2] performed needle biopsies on 76 patients suspected of having liver metastases. Eighteen false negative specimens were obtained as proved by subsequent operation or necropsy. Their rate of positive needle biopsies for metastatic carcinoma was 76%. On the basis of these data it may be anticipated that from two-thirds to three-fourths of metastatic liver lesions can be detected by blind needle biopsy. The yield of positive biopsies will be increased if the operator "aims" at liver nodules and repeats the punctures if the tissue obtained on the first and second trials is not suggestive of tumor on gross inspection.

CLINICAL PATTERN OF HEPATIC METASTASES. Weight loss of significant degree was noted by 31 (43%) of the 72 patients with metastases. It was surprising to find that abdominal pain, anorexia, nausea, fever, and malaise were infrequent complaints.

The outstanding physical abnormality was hepatomegaly, often of a marked degree. This was present in all but 5 patients (93%). The enlargement of the liver was often eccentric and accompanied by nodularity. Nodules that were tender to palpation often correlated histologically with necrosis of the tumor. Unlike the experience of Ward, *et al.*[22] who found that the probability for detecting metastatic carcinoma was the same whether the liver was smooth or nodular, we found metastases more readily in the nodular livers.

Ascites, edema and splenomegaly were found as late manifestations.

LABORATORY DATA. Although anemia has long been regarded as a common finding in metastatic disease, it was not a striking feature in this group. Mendelsohn and Bodansky[13] have also noted that hemoglobin levels are not significantly affected by metastases to the liver. The sedimentation rate was rapid in most cases, but offered no aid in differential diagnosis. Leukocytosis was present only occasionally.

Among the so-called liver function tests, serum alkaline phosphatase was found to be abnormal more often than any other test. It was studied in 69 of the 72 patients; it was elevated in 53 (77%). Alkaline phosphatase values above 30 King-Armstrong units were common. Others (Flood, Gutman and Gutman[6], Gibbons[7], Gutman *et al.*[9], Klotz[12], Mendelsohn and Bodansky[13], Meranze, Meranze and Rothman[14]) have reported hyperphosphatasemia to be present in from 65% to 93% of patients harboring hepatic metastases.

The sulfobromophthalein sodium retention test was performed in 22 nonicteric patients. The dye was retained in excess of normal in 17. Although the number of patients tested for increased retention of sulfobromophthalein sodium in this group of 72 patients is small, many of them responded abnormally. Both Gibbons[7] and Shay and Siplet[19] have pointed out that marked alterations in the alkaline phosphatase level and in the retention of sulfobromophthalein favor strongly a diagnosis of liver metastases.

Other liver function tests did not correlate well with the presence of intrahepatic metastases. Serum bilirubin was above normal in 20 cases (28%). It was usually only slightly elevated. Flocculation tests, plasma proteins, serum globulin patterns (Greenspan[8]), cholesterol concentration and serum glutamic oxaloacetic transaminase (Wroblewski, Jervis and LaDue[23]) deviated from normal in some patients, but not markedly, nor in a sufficient number for diagnostic purposes. Re-

cently Wroblewski[24] reported that in the presence of metastatic liver carcinoma both serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase tend to be elevated. When studied serially, serum glutamic oxaloacetic transaminase was consistently higher than serum glutamic pyruvic transaminase.

On the basis of our observation the constellation of signs and symptoms that suggests metastatic liver disease at the time patients enter the hospital consists of weight loss, an eccentrically enlarged nodular liver, hyperphosphatasemia and retention of sulfobromophthalein sodium. Jaundice is not a common symptom; if present, it is usually mild except when large bile ducts are obstructed.

COMPLICATIONS OF NEEDLE BIOPSY. In the entire series of 113 patients suspected to have intrahepatic metastases two serious complications developed. Both occurred in patients with metastatic carcinoma.

Case Reports. CASE 1.—R.T., male, 58 years, presented with weight loss, back pain and anorexia. Examination revealed slight jaundice and marked enlargement of a smooth nontender liver. There was no anemia. Occult blood was present in the stool. Serum alkaline phosphatase was 50 King-Armstrong units. Other liver function tests were noncontributory. Pre-biopsy studies for a latent bleeding tendency were within normal. Needle biopsy with the Terry instrument was performed by the transabdominal route into the right lobe of the liver. A satisfactory core of tissue was obtained with ease on the first trial. Six hours later the blood pressure fell precipitously, shock occurred and the abdomen became tender. Levophed, oxygen and blood transfusion were administered promptly. When bleeding failed to be controlled, operation was performed. The abdominal cavity was found to contain approximately 3½ L. of fluid and clotted blood. The anterior surface of the right lobe of the liver was the site of a 2 mm. puncture wound from which blood was issuing. The wound was sutured without difficulty and bleeding ceased. No metastases were present on the anterior aspect of the liver. However, a single 5 cm. mass of carcinomatous tissue projected from the inferior surface of the right lobe. This was biopsied surgically. The patient made an uneventful recovery. The surgical biopsy revealed adenocarcinoma; the needle biopsy revealed normal liver tissue.

CASE 2.—N.M., female, 57 years, presented with a history suggestive of biliary colic, recent enlargement of the abdomen and fever of several days' duration. Examination revealed a moderately enlarged nodular liver and inactive rheumatic heart disease. The only laboratory abnormalities were elevation of alpha globulin and a rapid sedimentation rate. Prebiopsy studies for a latent bleeding tendency were within normal. Needle biopsy with the Vim-Silverman instrument was performed by the transabdominal route into the enlarged nodular right lobe of the liver. A satisfactory core of tissue suspicious of carcinoma was secured without difficulty. About 36 hours after the biopsy had been performed abdominal pain and tenderness developed. Signs of a mild peritonitis and paralytic ileus evolved gradually. Conservative treatment was instituted and recovery was uneventful. The tissue obtained by needle biopsy revealed adenocarcinoma. Necropsy three months later revealed the primary carcinoma to be in the gallbladder.

Two other patients experienced minor hemorrhage. The transabdominal biopsy route was used in both. In one, a transient drop in blood pressure that corrected itself spontaneously was followed the next day by the development of a large ecchymosis of the lower abdominal wall. In the other, extensive ecchymoses appeared within 12 hours. It is assumed that major vessels of the abdominal wall muscles were pierced. The complications that attended needle biopsy are summarized in Table 3.

TABLE 3.—COMPLICATIONS ASSOCIATED WITH BLIND NEEDLE BIOPSY IN 72 PATIENTS WITH INTRAHEPATIC METASTASES

	Number
Deaths	None
Intraperitoneal hemorrhage	1
Peritonitis	1
Bleeding into abdominal wall	2

COMMENT. Metastatic carcinoma of the liver is a focal disease. It may seem surprising that two-thirds or more of metastatic lesions can be diagnosed by blind needle biopsy. This high yield reflects the fact that hepatomegaly of marked degree is present when most patients enter the hospital, and that biopsy is usually undertaken to confirm a well-founded clinical suspicion.

In the many instances where the site of a primary carcinoma was unknown in a patient suspected of having liver metastases we have performed liver biopsy as an early diagnostic procedure. Discovery of metastases has spared many patients from undergoing prolonged, tiring and expensive diagnostic procedures that otherwise would have been necessary. Early needle biopsy has often reduced the length of hospitalization and has obviated exploratory celiotomy.

Now that total hepatic lobectomy is being performed occasionally (Pack and Miller[16], Smith[20]), the demonstration of liver metastases by needle biopsy makes possible surgical palliation for some patients. Where both right and left lobes of the liver are involved by metastases, Roentgen irradiation has provided alleviation of symptoms (Phillips[17]).

Diagnostic information was obtained by needle biopsy in the presence of intrahepatic metastases with no greater incidence of complications than follows liver biopsy for other indications. This is the experience of most physicians (Bowden and Kravitz[2], Ward *et al.*[22], Zamchek and Klausenstock[25]). However, Fisher and Faloon[5] have recently reported a series of biopsies attended by an unusually high mortality rate. They recorded 5 deaths among 341 patients (1.5%), all associated with hemorrhage. Four of the 5 deaths occurred in a group of 33 patients with liver metastases. From this experience they concluded that the mortality rate of blind needle biopsy in the presence of hepatic metastases was 12%. They suggested that surgical biopsy under local anesthesia be substituted for blind needle biopsy in patients suspected to have liver metastases. Except for a single opinion (Karl[10]) that postbiopsy bleeding is more frequent in such patients, no other evidence could be found in the literature to favor the belief that biopsy is unduly hazardous in the presence of metastases.

In our group of 72 patients with intrahepatic metastases there were no fatalities.* Serious bleeding occurred in one patient and peritonitis developed in another. The peritonitis, presumably bacterial, was due to penetration of intestine during transabdominal biopsy; it was not related to the presence of liver metastases.

Ward *et al.*[22] had no deaths or serious complications among 66 patients with liver metastases subjected to needle biopsy. Bowden and Kravitz[2] recorded like experience with 76 patients.

Zamchek and Klausenstock[25] published an extensive review in 1953 of the world's literature dealing with blind needle liver biopsy. They analyzed the fatality rate among 20,016 cases and found that 17 deaths were related to the liver biopsy. Five deaths occurred in patients with metastatic liver disease. Only two of these were related to the biopsy procedure itself (Armed Forces Institute of Pathology[18], Volwiler and Jones[21]). Both were instances of uncontrollable hemorrhage. Of the other 3 who died, no coagulation studies were performed in 2 (Baron[1], Olivet[15]); in one of these,

*In addition to these 72 patients, 318 patients without intrahepatic metastases have had needle liver biopsies. There have been no deaths. Three patients required operation for postbiopsy complications: two for biliary peritonitis and one for intraperitoneal hemorrhage.

blood from the peritoneal cavity failed to clot on standing (Olivet[15]). The third patient died of peritonitis secondary to puncture of a subdiaphragmatic abscess with the biopsy needle (Olivet[15]). No chemotherapy was available at that time.

Study of the case histories presented by Fisher and Faloon[5] suggests that the association of postbiopsy hemorrhage and death may have been quite fortuitous in their patients with intrahepatic metastases. Two patients died after blood volume had been restored satisfactorily by transfusions, and at a time when vital signs were apparently stable. The cause of these 2 deaths was admittedly obscure. In another patient postbiopsy bleeding occurred into a large accumulation of ascites. At operation a biopsy puncture wound was found in a metastatic nodule. Suture was effected readily. Nonetheless, the patient went gradually downhill and died 5 days later. It is difficult to relate this fatality to bleeding *per se*. In another of their patients who bled profusely a 3 cm. laceration produced by the biopsy needle was found at operation. This was sutured with difficulty because the liver was friable. Secondary hemorrhage probably occurred 24 hours later and caused death. Laceration of the liver is one of the most feared accidents connected with blind needle biopsy. When it occurs it is usually due to the patient taking a deep breath unexpectedly while the biopsy instrument is being held rigidly. Laceration of liver parenchyma should be regarded as an accident related to technique rather than one related to the pathologic state of the liver.

Blind needle liver biopsy cannot be divorced entirely from risk. The dangers of the procedure can be minimized by careful selection of patients, adequate prebiopsy studies, adherence to contraindications and skillful technique. Taking into consideration the fact that not all deaths due to needle liver biopsy are reported, we believe that current data do not support the contention that liver biopsy performed in the presence of suspected liver metastases is considerably more hazardous than needle biopsy carried out for other proper indications.

Summary. 1. Blind needle liver biopsy was performed in 113 patients for the purpose of discovering intrahepatic neoplasm. Metastatic carcinoma was found in 72 patients (64%). Primary hepatic carcinoma was found in 4 patients.

2. At the time of admission to the hospital patients with metastatic liver disease often present a clinical pattern consisting of weight loss, eccentric enlargement of the liver with nodularity, hyperphosphatasemia and abnormal retention of sulfobromophthalein sodium.

3. Among the 72 patients with intrahepatic metastases, two serious complications developed after needle biopsy. One patient bled into the peritoneal cavity and required operation for control of hemorrhage; another developed mild peritonitis secondary to perforation of an abdominal viscus. Both patients recovered uneventfully.

4. Despite some suggestions to the contrary, the experience of most investigators indicates that blind needle liver biopsy performed in the presence of liver metastases carries essentially the same risk as biopsy for other accepted indications.

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SUMMARIO IN INTERLINGUA

Detection De Metastases Intrahepatic Per Biopsia A Agulia

1. Biopsias hepatic a agulia esseva effectuate in 113 patientes con le objectivo de discoperir neoplasmas intrahepatic. Carcinoma metastatic esseva trovate in 72 patientes (64%). Primari carcinoma esseva trovate in 4 patientes.

2. Al tempore del admission al hospital, patientes con metastatic morbo hepatic presenta frequentemente un tableau clinic consistente de perdita de peso, allargamento eccentric del hepate con nodularitate, hyperphosphatasemia e retention anormal de sulfobromophthaleina a natrium.

3. Inter le 72 patientes con metastases intrahepatic, duo serie complicationes se disveloppava post le biopsia a agulia. Un patiente sanguinava in le cavitate peritonee e requireva un operation pro subjugar le hemorrhagia. Un altere disveloppava un leve peritonitis secundari a perforation de un viscere abdominal. Ambes se restabliva sin incidente.

4. In despecto de certe assertiones contrari, le experientia del majoritate del investigatores indica que biopsia hepatic a agulia, effectuate in le presentia de metastases hepatic, curre essentialmente le mesme riscos como biopsias pro altere acceptate indicationes.

THE EFFECT OF ELECTRIC CONVULSIVE THERAPY ON SERUM LIPIDS*

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As part of a general study of blood lipids in psychiatric patients, the effect of electric convulsive therapy (ECT) on serum lipid levels was investigated. ECT is commonly used in the middle and older age groups where coronary atherosclerosis is so frequently present, and one of the recognized hazards of convulsive therapy in these individuals is acute coronary occlusion (Raskin and Johnson[16], Eyman and Morris[6], Jetter[10], Sisler and Wilt[20]). Consequently, it is of importance to know if significant serum lipid alterations follow convulsive electric shock, with possible subsequent aggravation of preexistent coronary artery disease, particularly in individuals receiving a series of shocks. Also, two stressful situations occur in the patient receiving ECT. The first is the anxiety aroused by the knowledge of the approaching shock treatment and the second is the convulsion itself. Thus, an experiment presents itself in which the effect of emotional stress and physiological stress on blood lipids can be studied.

The effect of electroshock therapy on blood cholesterol was studied by Bonati *et al.*[4], who found a slight average lowering which they did not consider significant. Van der Beek[2] studied serum cholesterol changes after electronarcosis therapy and found an average increase of 6% in 39 of 48 determinations and a decrease in 9. In our patients, total serum cholesterol, lipid phosphorus, and alpha and beta lipoproteins were determined in an attempt to get a more complete picture of the blood lipids as affected by ECT.

Method of Study. Fourteen hospitalized psychiatric patients were studied. The psychiatric diagnosis was schizophrenia in 10 patients and depression in 4 patients. The ages ranged from 16 to 62; there were 9 male and 5 female subjects. All blood samples were taken in the fasting state with the following procedure. The first sample was obtained at least one day and as long as 15 days before electroshock therapy was given. A second blood sample was taken on the morning of therapy, 1 to 2 hours before the electroshock was administered. At this time, all the patients were aware that they were to receive electroshock therapy. The third blood sample was taken approximately 15 minutes to 2 hours after the cessation of the convulsion. The fourth sample was taken on the morning of the following day.

Total serum cholesterol was determined by a modification of the method of Abell *et al.*[1]. Lipid phosphorus was obtained by the method of Youngburg and Youngburg[23] using the phosphate procedure of Fiske and Subbarrow[7]. Alpha and beta lipoproteins were determined by a modification of the method of Jencks and Durrum[9]. All determinations were made in duplicate.

Results. Because of the technical error inherent in the determination of serum cholesterol (Lawry *et al.*[12],

*This work was aided by a grant from the National Institutes of Health H141(C8). the Heart Association of Southeastern Pennsylvania, and Eli Lilly Company of Indianapolis, Indiana.

Lewis *et al.*[13]), and because of normal intra-day and day-to-day cholesterol variations in any individual (Shapiro, Estes and Hilderman[19], Thomas and Eisenberg[21]), changes of 10% or less were not considered significant. Lipid phosphorus and lipoprotein changes of 10% or less were also not considered significant.

Inasmuch as the dietary habits of our patients before admission were not known, the control values of the lipids were obtained by using the mean of the first and fourth blood sample determinations. This was done to minimize any effects on the serum lipid levels which might result from a marked diet change in a patient from his pre-admission eating habits to the hospital diet.

Table 1 shows the serum lipid values of the subjects studied. Relatively few of the patients showed a significant change in their serum lipids either on the morning of ECT (anticipation of shock therapy) or after the actual convulsion. Four of the 14 patients showed changes in total cholesterol in their blood taken just before shock therapy as compared to their control levels. Two increased significantly and two decreased. Two subjects showed a rise in lipid phosphorus and one showed a lowering. Two patients had a significant reduction in their beta-lipoprotein levels. Following the convulsion, one patient showed a significant increase in cholesterol and 2 showed a decrease as compared to the pre-convulsion level. Two patients showed a reduction in lipid phosphorus. One patient had an increase and one a decrease in beta-lipoprotein. The remaining subjects showed no significant lipid changes. The results are summarized in Table 2. The degree of change of any of the lipids did not appear to be related to the original control level; that is, whether it was normal or elevated.

Discussion. The absence of significant increases in serum lipids as a consequence of ECT, in the majority of instances, would tend to lessen the fear of the shock therapy adversely affecting pre-existent coronary atherosclerosis. While the threat of acute coronary occlusion and myocardial infarction always exists following convulsive therapy in an individual with coronary artery disease, our results indicate that usually no significant lipid changes occur which might be considered a factor in the aggravation of pre-existent coronary artery disease.

THE EFFECT OF EMOTIONAL STRESS. Wertlake *et al.*[22] and Rosenman and Friedman[17] found that continuous emotional stress caused significant increases in serum cholesterol levels. Cathey[5] and Groover[8] have similarly noted increases in serum cholesterol in a large percentage of their patients as a result of emotional stress. The emotional stress of anticipating ECT did not significantly affect the blood lipid levels in the majority of our patients. The absence of such effects in most of our cases could be due to two factors. First, our patients were all psychiatric cases, suffering from schizophrenia or depression. The emotional responses in these individuals could not be considered normal regardless of overt manifestations; hence, it is difficult to know how deeply they were disturbed by the anticipation of ECT. Second, the stress situation was of short duration and possibly too transient to cause a blood lipid change. This was suggested by Beischer[3] as an explanation for his failure to find significant lipid changes following "mental stress" in his human centrifuge ride and low pressure chamber studies which were done in normal subjects.

THE EFFECT OF PHYSICAL AND PHYSIOLOGICAL STRESS. In spite of the marked physical and physiological stress involved in the electroshock convulsion,

TABLE 1.—TOTAL SERUM CHOLESTEROL, LIPID PHOSPHORUS AND BETA LIPOPROTEIN LEVELS* IN PSYCHIATRIC PATIENTS BEFORE AND AFTER ELECTRIC CONVULSIVE THERAPY

				Control			*Before Electroshock*			*After Convulsion*		
Subject	*Age*	*Sex*	*Psychiatric Diagnosis*	*Total Cholesterol* mg./100 ml.	*Lipid P* mg./100 ml.	*Beta Lipoprotein* %	*Total Cholesterol* mg./100 ml.	*Lipid P* mg./100 ml.	*Beta Lipoprotein* %	*Total Cholesterol* mg./100 ml.	*Lipid P* mg./100 ml.	*Beta Lipoprotein* %
1	26	M	Schizophrenia	307	12.0	84.0	300	12.2	88.0	327	11.8	83.2
2	39	F	Schizophrenia	241	12.2	73.6	242	12.2	72.9	246	12.6	72.9
3	44	F	Schizophrenia	155	8.2	83.2	149	8.5	76.2	177	8.0	81.1
4	22	F	Schizophrenia	206	8.9	74.0	252	10.0	73.8	224	10.4	66.0
5	30	M	Schizophrenia	244	9.3	81.1	240	10.2	68.3	233	10.6	74.4
6	41	F	Depression	153	9.0	80.9	156	9.7	68.7	143	9.3	66.3
7	16	F	Depression	149	10.5	71.4	128	10.0	67.3	136	10.5	63.1
8	34	M	Schizophrenia	225	10.1	69.2	211	10.9	71.6	179	8.6	66.7
9	23	M	Schizophrenia	219	8.8	73.8	202	9.6	70.0	212	8.7	72.7
10	22	M	Schizophrenia	195	9.7	79.6	218	10.9	71.4	219	11.0	74.5
11	45	M	Depression	260	10.2	79.1	270	10.6	79.3	265	10.4	72.7
12	62	M	Depression	220	10.1	65.9	227	9.4	70.5	242	8.4	73.7
13	38	M	Schizophrenia	211	9.0	83.1	182	7.5	80.8	181	7.5	80.0
14	28	M	Schizophrenia	289	10.0	84.2	267	10.2	77.2	284	11.3	86.5

*All values represent the mean of duplicate determinations.

TABLE 2.—EFFECT OF ANTICIPATION OF ELECTRIC CONVULSIVE THERAPY (ECT) AND ACTUAL CONVULSION ON SERUM LIPID LEVELS

	Total Cholesterol		*Lipid Phosphorus*		*Beta Lipoprotein*	
	Anticipation of ECT	*Convulsion*	*Anticipation of ECT*	*Convulsion*	*Anticipation of ECT*	*Convulsion*
Number of subjects with significant* increase	2	1	2	0	0	1
Number of subjects with significant decrease	2	2	1	2	2	1
Number of subjects with no significant change	10	11	11	12	12	12

*A change in serum lipid level of more than 10% was considered significant.

no significant lipid changes ensued in most of our patients. This is contrary to observations reported in other types of studies of stress effects on blood lipids. Kuhl and associates[11] found that immersion in cold water caused an increase in serum cholesterol, although Mann[14] reported various physiological stresses caused a decrease in serum cholesterol. Selye[18] recognizes a biphasic response of serum lipids in his general adaptation syndrome. In our patients, the convulsion effects on the serum lipids could, in part, be due to the physical exertion involved (Nadeau and Larue[15]). This, in turn, could modify, and possibly counterbalance, serum lipid effects of the convulsion which might result from adrenocortical or adrenomedullary stimulation. The more consistent cholesterol elevations in Van der Beek's[2] electroshock patients as compared to ours might be explained by the lack of physical exertion effects in his subjects, all of whom received electronarcosis which involves a more gradual shock and no convulsion.

Summary and Conclusions. 1. The effect of electric convulsive therapy on serum cholesterol, phospholipids, and lipoproteins was studied in 14 psychiatric patients.

2. No significant change in serum lipid levels was found in the majority of our subjects, either as a result of anticipating electric convulsive therapy or of the actual convulsion.

3. Our findings are discussed in relation to the effects of emotional and physiological stress on serum lipids.

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(Interlingua on page 334)

A COMPARISON OF THE LATEX FIXATION-WHOLE SERUM, LATEX FIXATION-EUGLOBULIN FRACTION AND BENTONITE FLOCCULATION TESTS IN THE LABORATORY DIAGNOSIS OF RHEUMATOID ARTHRITIS*

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There has long been a need for a definitive laboratory procedure to confirm the diagnosis of rheumatoid arthritis. For the most part, this diagnosis has been based entirely on clinical findings and the known characteristics of the disease. Obviously, in early stages or with atypical manifestations of the disease the diagnosis may often be long delayed. This fact has frequently resulted in delayed institution of therapy with possible resultant prolongation of disability.

It had been recognized as early as 1930 that the serum from individuals with rheumatoid arthritis would agglutinate the streptococcus organism (Cecil, Nicholls and Stainsby[5]). Originally this finding was interpreted as a clue to the elusive etiology of the disease. It soon became apparent, however, that this reaction lacked specificity; that the serum would agglutinate other bacteria and sensitized bodies as well. Researchers have recently reinstituted studies of this agglutination phenomenon with a direct study of the serum protein resulting in such a reaction. It is possible that, though long delayed, this will still offer the best approach to unraveling the mystery of the cause of rheumatoid arthritis.

Several attempts to utilize this agglutination phenomenon as a diagnostic test in rheumatoid arthritis were originally made but practically abandoned because of the low incidence of positive reactions. In 1940, Waaler[19], and in 1948, Rose, Ragan, Pearce and Lipman[14] devised an agglutination test for rheumatoid arthritis using sensitized sheep red cells. Again, the relatively low incidence of positive reactions, especially in early and mild cases,

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led to a lack of enthusiasm for the acceptance of the Waaler-Rose test as a routine diagnostic procedure in rheumatoid arthritis.

Recently there have been described several laboratory procedures which are proving of value in the serologic diagnosis of rheumatoid arthritis. The latex fixation test using whole serum was described by Singer and Plotz in 1956[17]. The latex fixation using euglobulin fraction was first described by Craig, Kerby and Persons[6]. More recently the Bentonite flocculation test has been described (Bozicevich[3]). This study was undertaken to compare the relative sensitivity of these three procedures in the laboratory diagnosis of rheumatoid arthritis.

The serological reactions used in these laboratory phenomena all depend on the presence in serum of a high molecular weight protein called the "rheumatoid factor." The exact nature of this factor remains unknown as to mechanism of its elaboration, chemical structure and pathological significance. However, it has been identified on electrophoretic and ultracentrifuge patterns and there is a recent report of isolation of this factor by Svartz *et al.* of Sweden[18]. It appears to be confined principally to the gamma globulin fraction of the serum. The known affinity of the rheumatoid factor for gamma globulin forms the basis for the agglutinating activity.

Materials and Methods. SUBJECTS STUDIED. A total of 76 patients with a clinical diagnosis of rheumatoid arthritis were included in this study. These patients were selected from the Hillman Arthritis Clinic and from the teaching service of the University Hospital. The criteria of the American Rheumatism Association were maintained in establishing the diagnosis in these patients. For the purpose of this study a positive agglutination test was not considered as one of the diagnostic criteria. There was a preponderance of females in a ratio of approximately 2 to 1. Their ages ranged from 19 to 72 years. Also included are 9 patients whose disease is certainly suggestive clinically of rheumatoid arthritis, but in each of whom there was some question as to the diagnosis. We have grouped these together under the designation of atypical rheumatoid arthritis. In addition, we have studied 71 patients who had musculoskeletal disease other than rheumatoid arthritis and they were classified under 11 separate diagnostic categories (Table 1).

TABLE 1.—NUMBER OF POSITIVE REACTORS IN ALL GROUPS USING THE WHOLE SERUM LATEX FIXATION TEST.

	Latex Fixation—Whole Serum								
	No. Tested			*No. Positive*			*% Positive*		
Disease	*M*	*F*	*T*	*M*	*F*	*T*	*M*	*F*	*T*
Rheumatoid Arthritis (definite)	27	49	76	22	34	56	81	69	74
Rheumatoid Arthritis (atypical)	2	7	9	0	0	0	0	0	0
Rheumatoid Spondylitis	9	1	10	0	0	0	0	0	0
Reiter's Syndrome	1	0	1	0	0	0	0	0	0
Still's Disease	2	1	3	0	0	0	0	0	0
Sjogren's Syndrome	0	3	3	0	0	0	0	0	0
Osteoarthritis	7	24	31	0	0	0	0	0	0
Systemic L. E.	1	9	10	0	1	1	0	11	10
Gout	2	0	2	0	0	0	0	0	0
Scleroderma	1	1	2	0	0	0	0	0	0
Shoulder-Hand Syndrome	1	3	4	0	0	0	0	0	0
Infectious Arthritis	2	2	4	0	0	0	0	0	0
Rheumatic Fever	0	3	3	0	0	0	0	0	0

PROCEDURE. The latex fixation test was performed according to the method of Singer and Plotz[17]. This test substitutes antigenically

inert latex particles for the customarily used sheep erythrocytes as carriers of some component of gamma globulin. The 1 to 20 dilution was arbitrarily selected and results are reported simply as negative or positive. The latex particle size was 0.8140 microns. Fraction II lypholyzed human gamma globulin served as the sensitizing agent.

A positive and negative control was included with each group of sera tested. Agglutination was considered to be present if the supernatant was relatively clear after centrifuging and agglutinated particles could be seen with a hand lens after gentle agitation. More recently we have employed the Hyland* slide method as a simplification of this procedure.

culation of 2 plus or greater occurs at or above a dilution of 1:32.

Results. The results of the latex fixation procedure using whole serum are summarized in Table 1. Of the 76 patients with an established clinical diagnosis of rheumatoid arthritis, 56 (74%) were positive reactors with the latex fixation procedure using whole blood serum. An analysis of the results of the test based on sex revealed that 81% of the males showed positive reactions while only 69% of the females were positive reactors.

TABLE 2.—NUMBER OF POSITIVE REACTORS IN ALL GROUPS USING THE EUGLOBULIN LATEX FIXATION TEST.

	Latex Fixation—Euglobulin Fraction								
	No. Tested			*No. Positive*			*% Positive*		
Disease	*M*	*F*	*T*	*M*	*F*	*T*	*M*	*F*	*T*
Rheumatoid Arthritis (definite)	27	49	76	24	41	65	89	84	86
Rheumatoid Arthritis (atypical)	2	6	8	0	0	0	0	0	0
Rheumatoid Spondylitis	8	1	9	0	0	0	0	0	0
Reiter's Syndrome	1	0	1	0	0	0	0	0	0
Still's Disease	1	1	2	0	0	0	0	0	0
Sjogren's Syndrome	0	3	3	0	1	1	0	33	33
Osteoarthritis	4	16	20	0	0	0	0	0	0
Systemic L. E.	0	7	7	0	1	1	0	14	0
Gout	2	0	2	0	0	0	0	0	14
Scleroderma	1	1	2	0	0	0	0	0	0
Shoulder-Hand Syndrome	0	2	2	0	0	0	0	0	0
Infectious Arthritis	2	2	4	0	0	0	0	0	0
Rheumatic Fever	0	2	2	0	0	0	0	0	0

Euglobulin fractionation was performed at pH 6.1 to 6.4 using the method of Craig, Kerby and Persons[6]. The serum is diluted with 0.0027 HCl and precipitated at 4° C. for 45 minutes followed by cold centrifugation, and finally diluted back to the original volume with 0.9% saline. The latex test as outlined above was carried out on the resultant solution.

The Bentonite flocculation test was carried out as described by Bozicevich, *et al.*[3]. In this procedure the suspended particles of Wyoming Bentonite clay are obtained by selective gravity for uniform size. These are sensitized with Fraction II lyophilized gamma globulin and incorporated in a 2-fold serial dilution, dropslide flocculation. This can be interpreted microscopically as positive if floc-

None of the patients with atypical rheumatoid arthritis showed a positive reaction. Of the other musculoskeletal disorders included in the study, only one patient with systemic lupus erythematosus gave a positive test.

The results of the latex fixation procedure using the euglobulin fraction are summarized in Table 2. The sera of the same 76 patients with rheumatoid arthritis previously described were examined. This procedure gave an increase in the positively reacting rheumatoid sera from 74% to 86%. Again, a greater number of males had positive

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reactions. Likewise, this procedure failed to detect any positively reacting sera among the 9 patients with atypical findings but suggestive of rheumatoid arthritis tested; however, one patient with Sjorgren's syndrome gave a positive reaction.

The results using the Bentonite flocculation test are summarized in Table 3. The sera of the same 76 patients were examined employing this method and an augmentation of positive reactors to 88% was noted. None of the so-called atypical rheumatoid arthritis showed any positive reactions. However, an additional patient with systemic lupus erythematosus showed a positive reaction and 2 of the 3 patients previously diagnosed as shoulder hand syndrome were positive reactors.

TABLE 3.—NUMBER OF POSITIVE REACTORS IN ALL GROUPS USING THE BENTONITE FLOCCULATION TEST.

	Bentonite Flocculation								
	No. Tested			*No. Positive*			*% Positive*		
Disease	*M*	*F*	*T*	*M*	*F*	*T*	*M*	*F*	*T*
Rheumatoid Arthritis (definite)	27	49	76	25	42	67	93	86	88
Rheumatoid Arthritis (atypical)	2	6	8	0	2	2	0	33	25
Rheumatoid Spondylitis	8	1	9	0	0	0	0	0	0
Reiter's Syndrome	1	0	1	0	0	0	0	0	0
Still's Disease	1	1	2	0	0	0	0	0	0
Sjogren's Syndrome	0	3	3	0	1	1	0	33	33
Osteoarthritis	5	15	20	0	0	0	0	0	0
Systemic L. E.	0	8	8	0	2	2	0	25	25
Gout	2	0	2	0	0	0	0	0	0
Scleroderma	1	1	2	0	0	0	0	0	0
Shoulder-Hand Syndrome	0	3	3	0	2	2	0	67	67
Infectious Arthritis	2	2	4	0	0	0	0	0	0
Rheumatic Fever	0	2	2	0	0	0	0	0	0

Comment. The patients with a clinical diagnosis of rheumatoid arthritis who showed an agglutinating activity in none of the 3 tests applied are being subjected to a latex inhibition procedure as described by Hall, Mednis and Bayles[9]. It is possible that such testing may reduce the size of this group. Certainly as more information is accumulated concerning the rheumatoid factor, especially of the influence of duration, severity and treatment of the disease, we may expect a more definitive understanding of the disease and the reasons for the presence of positive and negative reacting activity. Certainly it is possible that the euglobulin fractionation achieves only partial and possibly, in some instances, insufficient separation of the agglutinating factor from its inhibitors as suggested by Ziff *et al.*[21].

Confirming the observation of Olsen and Rantz, female patients with definite clinical evidence of rheumatoid arthritis had negative tests more frequently than comparative males[12]. These authors suggested the possibility of a different disease occurring in middle-aged women which is characterized by painful, symmetrical joint swelling.

We have not attempted to make any definite studies in establishing correlation between activity of the disease and titers of the agglutinations. This particular point has been pursued by several workers, some attaining good correlation (Brown, Bunim and McEwen[4], Heller, Jacobson and Kalodna[10], Rose *et al.*[14]) and some others

not (Alexander and deForest[1], Bell[2], Scott[16]). The basis for the discrepancies would seem to be due to small series in most reports, inadequately defined criteria of activity and insufficiently sensitive methods.

In this series no agglutinating activity was found in sera from patients with osteoarthritis, ankylosing spondylitis, gouty arthritis, Reiter's syndrome, Still's disease, scleroderma, infectious arthritis, and rheumatic fever. Moreover, it is generally believed that the over-all incidence of positivity in other conditions than rheumatoid arthritis, such as systemic lupus erythematosus, scleroderma, and periarteritis nodosa, is somewhat less than 34%, and most of these cases were conditions closely related to rheumatoid arthritis (Ziff[20]). Several authors have reported positive tests in diseases other than rheumatoid arthritis, using, for the most part, only one serologic test. Ziff and associates[20] have noted a 16% incidence of positives in patients with infectious hepatitis. Others (Peltier and Christian[13], Rothermich and Philips[15]) have found positive serologic reactions in patients with syphilis as well as in trichinosis (Epstein, Engleman and Ross[8]), and rheumatic heart disease (deForest, Mucci and Boisvert[7]). More recently, Kunkel, Simon and Fudenberg[11] have found positive latex and precipitive tests in patients with sarcoidosis, kala-azar and cirrhosis of the liver, all apparently without clinical manifestations of rheumatoid arthritis.

All this information is of interest in evaluating the clinical picture with the laboratory test for the diagnosis of the disease, bearing in mind that the several tests now in current use vary in complexity, specificity and sensitivity.

Summary. This study compares the number of positive and negative serological tests for rheumatoid factor obtained using the whole serum latex fixation method, the euglobulin latex fixation method, and the Bentonite flocculation method.

Included in the study were 76 patients who met the criteria of the American Rheumatism Association for definite rheumatoid arthritis, 9 patients with disease clinically suggestive of rheumatoid arthritis, but not fulfilling the ARA criteria, designated as atypical rheumatoid arthritis, and 71 patients with musculoskeletal disease other than rheumatoid arthritis.

Sera from all patients of each group were tested by the whole serum latex fixation method, the euglobulin latex fixation method, and the Bentonite flocculation method.

Of the 76 patients with an established diagnosis of rheumatoid arthritis 74% showed positive reactions by the whole serum latex fixation procedure. When the number of positive reactors in this group were analyzed according to sex it was found that 81% of the males were positive but only 69% of the females were positive. None of the patients with atypical rheumatoid arthritis showed a positive reaction by this method, and of the group with other musculoskeletal disease only one patient with systemic lupus erythematosus gave a positive test.

Using the euglobulin latex fixation procedure, 86% of the definite rheumatoid arthritics gave a positive result. No patient with atypical rheumatoid arthritis gave a positive test and from the group of patients with other musculoskeletal disease one patient with Sjogren's syndrome gave a positive result.

Employing the Bentonite flocculation method, 88% of the patients with definite rheumatoid arthritis gave positive results. There was no positive test among the group with atypical rheumatoid arthritis. In the group with other musculoskeletal disease, however,

another patient with systemic lupus erythematosus and 2 of 3 patients previously diagnosed as shoulder hand syndrome were positive reactors.

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SUMMARIO IN INTERLINGUA

Un Comparation Del Diagnoses Laboratorial De Arthritis Rheumatoide Per Le Test Del Fixation A Latex Con Sero Total, Le Test Del Fixation A Latex Con Le Fraction Euglobulinic, E Le Test Del Flocculation A Bentonite

Le presente studio compara le numeros del positive e negative tests serologic pro factor rheumatoide que es obtenite per le methodo de fixation a latex con sero total, le methodo de fixation a latex con euglobulina, a le methodo de flocculation a bentonite.

Esseva includite in le studio (1) 76 patientes qui satisfaceva le criterios del Association American de Rheumatologia pro definite arthritis rheumatoide, (2) 9 patientes con un morbo clinicamente suggerente arthritis rheumatoide sin satisfacer le criterios del AAR (hic designate como atypic arthritis rheumatoide), e (3) 71 patientes con un morbo musculoskeletic altere que arthritis rheumatoide.

Seros ab omne le patientes in omne le gruppos esseva testate per omne le tres methodos mentionate.

Inter le 76 patientes con un establite diagnose de arthritis rheumatoide, 74% manifestava positive reactiones per le methodo de fixation a latex con sero total. Quando le numero del reactores positive in iste gruppo esseva analysate secundo

le duo sexos, il esseva trovate que 81% del masculos esseva positive sed solmente 69% del femininas. Nulle del patientes con atypic arthritis rheumatoide manifestava un reaction positive per iste methodo, e in le gruppo de altere morbos musculoskeletic, solmente un patiente (con systemic lupus erythematose) habeva un test a resultato positive.

In le caso del methodo de fixation a latex con euglobulina, 86% del patientes con definite arthritis rheumatoide monstrava resultatos positive. Nulle patiente con atypic arthritis rheumatoide monstrava positivitate in iste test, e inter le patientes con altere morbos musculoskeletic, un sol, con le syndrome de Sjogren, esseva positive.

In le caso del methodo de flocculation a bentonite, 88% del patientes con definite arthritis rheumatoide monstrava resultatos positive. Nulle test esseva positive in le gruppo de patientes con atypic arthritis rheumatoide. Tamen, in le gruppo con altere morbos musculoskeletic, un secunde patiente con systemic lupus erythematose e 2 de 3 patientes previemente diagnosticate como suffrente de syndrome de spatula e mano esseva reactores positive.

ACUTE PERICARDITIS AS THE INITIAL MANIFESTATION OF INFECTIOUS MONONUCLEOSIS

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Idiopathic pericarditis, first described over a century ago (Christian[5]), is being recognized rather frequently at the present time. In spite of this, however, little progress has been made in clarifying its etiology. Recently a patient was encountered who presented with acute pericarditis, at the time presumably idiopathic, but who, 10 days after the first symptoms, developed the clinical picture of severe infectious mononucleosis. Because of the paucity of recorded instances of this association, this case is being reported.

Case Report. R.J., a 22-year-old man, was seen at the Maury County Hospital emergency room the evening of June 2, 1957, complaining of severe substernal pain radiating to the left arm. This pain had first been noted 2 days previously. It was of gradual onset and of a dull, steady character, beginning beneath the middle and lower sternum and being present also in the inner aspect of the left arm as far as the fourth and fifth digits. It had been noted that deep inspiration markedly aggravated the pain.

The day before admission, the patient saw a physician who found his temperature 102° F., diagnosed "flu," and administered antibiotics and analgesics. The pain continued in remissions and exacerbations the remainder of that day, that night, and the day of admission. It gradually became excruciating in character, and the patient sought relief at the hospital emergency room. He had found that he was most comfortable reclining at an angle of 45°. There had been no respiratory or other symptoms of note. Past history revealed no significant illnesses.

Physical examination revealed a pale, perspiring, sthenic young man groaning from severe pain. Temperature was 99° F.; pulse, 70; respiration, 22; blood pressure, 120/90. The skin was clammy; there was no cyanosis. The head, eyes, ears, nose, and throat were negative. There was no venous distention nor lymphadenopathy. The trachea was midline and the neck supple. The lungs were clear. The heart was of normal size and regular, except for mild respiratory arrhythmia. The heart tones were mildly muffled; no murmurs nor pericardial friction rub were audible. The abdomen and extremities were not remarkable. An electrocardiogram taken at the time showed an S–T segment elevation of 2 mm. in leads I, V_5 and V_6, with a lesser elevation in leads II, aVL, aVF, and V_4, and a 2 mm. S–T depression in aVR (Fig. 1). The electrocardiographic diagnosis of acute pericarditis was made.

Laboratory studies the next day revealed a white blood count of 6,500, with 44% polymorphonuclears, 52% lymphocytes, and 4% monocytes, some of the lymphocytes appearing atypical. The hemoglobin was 15.4 gm.; hematocrit, 49; sedimentation rate, 20 mm. per hour; urinalysis, negative.

During the first 8 hospital days the patient had an irregular temperature of 98.6° to 100.6° F. The blood pressure, pulse, and respirations were in the normal range. Following initial relief from pain, the patient had little discomfort until the fourth hospital day when pain became very severe, requiring large amounts of narcotics over a period of 24 hours. A chest film on the third hospital day was normal. An electrocardiogram on this date showed the S–T segments still somewhat elevated in the leads previously noted, followed by inversion of the T waves in all these leads. aVR showed S–T slightly depressed with an upright T (Fig. 2). An electrocardiogram on the seventh hospital day was within normal limits. The first and second strength tuberculin tests were negative, as was the histoplasmin test. During the first 8 hospital days, the physical examination remained consistently negative. The patient felt well from the fifth through the seventh hospital days.

On the eighth day the severe chest pain recurred, again worse on inspiration and radiating to the left arm, and again requiring large amounts of narcotics. It persisted until the eleventh hospital day and thereafter did not recur. On the ninth day his temperature

rose to 104° F., and it remained from 102° to 104° F. for the next two days, gradually thereafter returning toward normal. At the same time the patient complained of a very sore throat, with extreme discomfort on swallowing. It was noted that the posterior soft palate, uvula, tonsillar pillars, and pharynx were all fiery red without a membrane. The cervical glands became markedly swollen and tender, the axillary glands moderately so. glutination was positive in a titre of 1:896; cold agglutins were positive 1:4. By the tenth day the patient's rash had spread to cover the extremities, the neck, and the face, the macular lesions being quite dense on the torso and proximal extremities, less dense on the distal extremities and face, and absent on the palms and soles. Numerous lesions on the back developed hemorrhagic centers. The lesions were moderately pruritic.

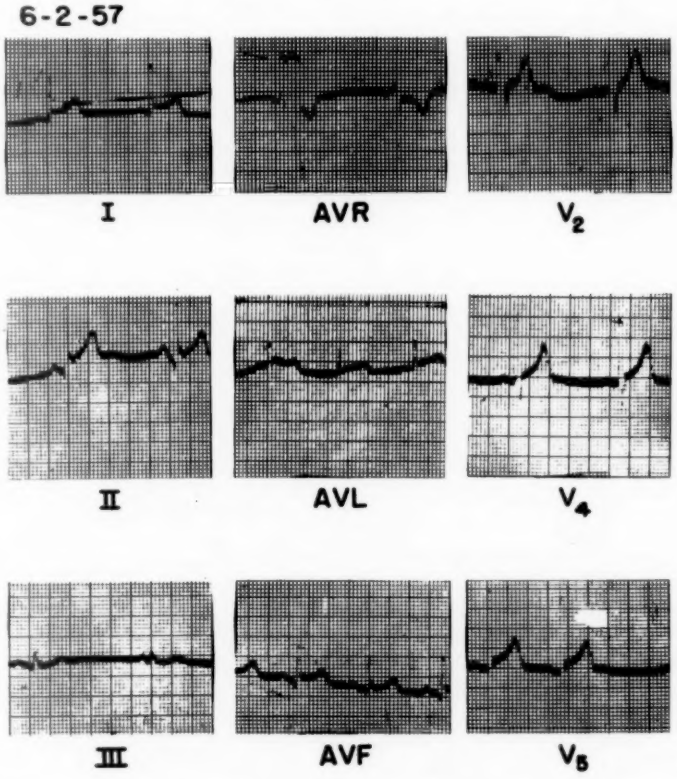

Fig. 1.—Admission electrocardiogram showing concave S–T elevations in leads I, II, aVL, aVF, V_4 and V_5, with S–T depression in aVR.

The lungs remained clear, the heart normal on auscultation. Also on the ninth day, a salmon-colored, macular rash appeared on the chest, abdomen and back. On the same date the white blood count was 28,600 with 24% segmented polymorphonuclears, 14% stab forms, 59% lymphocytes, and 1% monocytes. It was noted that 98% of the lymphocytes appeared atypical. The platelets appeared reduced. Also on this date the heterophil ag-

On the eleventh day the patient began to improve and he felt well thereafter. His sore throat and swollen tender glands rapidly subsided, his temperature returned gradually toward normal, the chest pain did not recur, and his rash slowly faded. An electrocardiogram on the eleventh hospital day again showed changes consistent with a subacute pericarditis; namely, S–T segment elevation in leads II and aVL and inverted T waves in

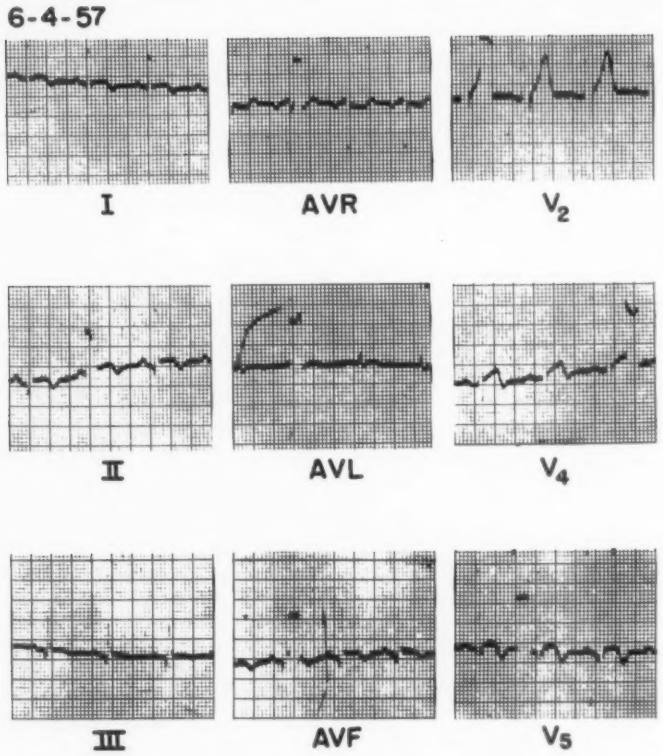

Fig. 2.—An electrocardiogram on the third day showing a return of the S–T segments toward normal with T wave inversions in the same leads and upright T waves in aVR.

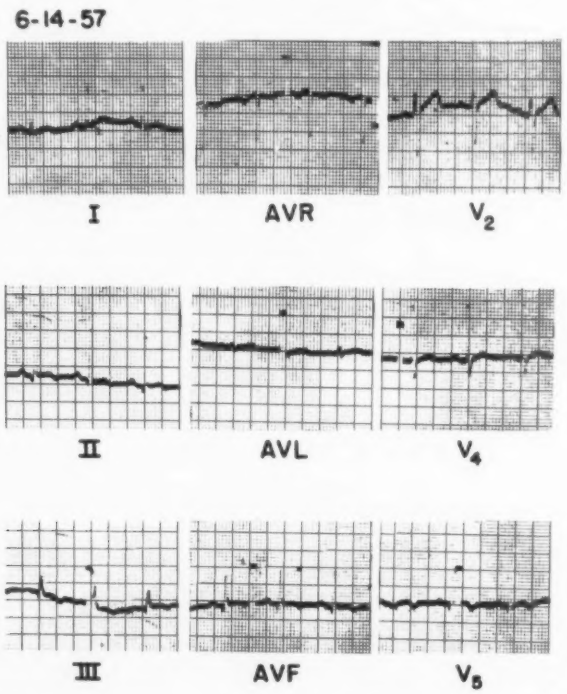

Fig. 3.—An electrocardiogram on the eleventh day, following a normal tracing (not shown) on the seventh day. S–T elevations are seen in II and aVL with T wave inversion in II, III, aVF and V_5.

leads III, V_5, V_6 and aVF (Fig. 3). On the seventeenth hospital day, at the time of discharge, the patient was asymptomatic. Physical examination at that time was normal except for a slight rash which persisted on the torso. On this date the white blood count was 7,300, with 33% polymorphonuclears, 59% lymphocytes, 3% monocytes and 5% eosinophils. Sixteen per cent of the lymphocytes were still classed as atypical. The heterophil titre on this date was 1:224. It is to be noted that a pericardial friction rub was never heard, although it was repeatedly listened for with the patient in various positions.

When seen at the office 11 days following discharge, the patient felt well, though still weak. His weight was 137 lbs., 27 lbs. less than one month previously. Physical examination and blood studies were normal. When seen again 2 weeks later he was feeling well, gaining weight, and moderately active. Examination and electrocardiogram at this time were normal (Fig. 4).

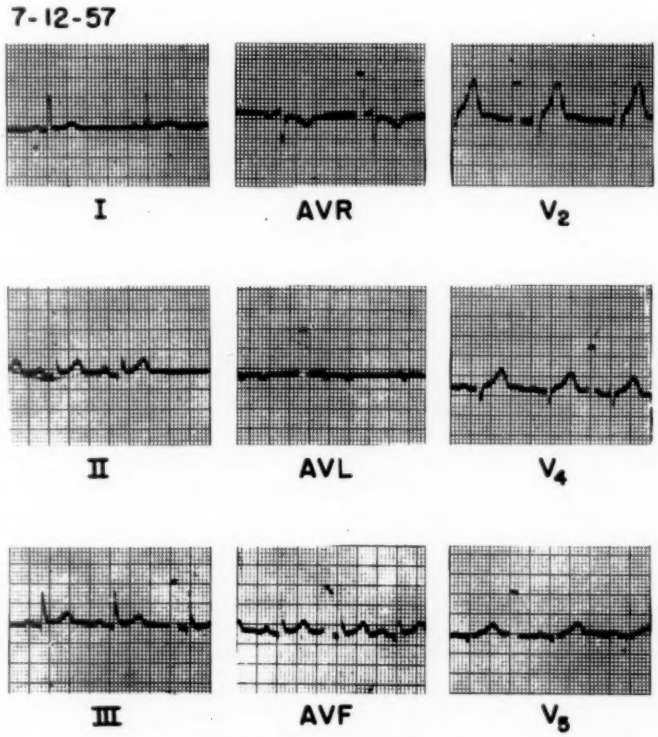

Fig. 4.—Electrocardiogram 6 weeks after onset of illness showing a return toward normal.

Discussion. Idiopathic pericarditis is a benign condition of acute type, lasting from a few weeks to several months, prone to relapses (Tomlin, Logue and Hurst[33]), but nearly always ending in complete recovery. The etiology of idiopathic pericarditis remains obscure. Several cases have been reported associated with primary atypical, or virus, pneumonia (Evans[10], Finkelstein and Klainer[12], Fuller and Quinlan[13], Wolff[36]). Numerous cases have been associated with upper respiratory infections, at least many of which have been presumably viral in type (Carmichael *et al.*[3], Evans[10], Levy and Patterson[18], Nathan and Dathe[25], Reid *et al.*[26]). Cases have been associated with other

viral, or presumably viral, diseases of a more generalized type, notably infectious mononucleosis (Célice *et al.*[4], de Fazio and Marsico[8], Evans and Graybiel[11], Kramer[16], Miller, Uricchio and Phillips[22], Roseman and Barry[27], Shugoll[29], Soloff and Zatuchni[31]), lymphogranuloma venereum (Sheldon *et al.*[28]), epidemic myositis (Bing[1]), Reiter's syndrome (Csonka and Oates[6]), and Coxsackie virus infection (Weinstein[35]). Cases have also been reported associated with tonsillitis (Morison[23], Nathan and Dathe[25]), presumably bacterial, and certain of the other upper respiratory infections previously noted (Carmichael *et al.*[3], Evans[10], Levy and Patterson[18], Nathan and Dathe[25], Reid *et al.*[26]) may have been primarily bacterial in type. The theory has been advanced that contact transmission may occur (Bing[1], Evans[10]). That a few cases of acute pericarditis are allergic in etiology is well-documented (Harkavy[14], McKinlay[20], Zivitz and Oshlag[37]). In these instances, however, eosinophilic pleural effusions, pulmonary infiltrates, and other manifestations of allergy have been striking. A few instances of acute pericarditis have been reported following operations not involving the heart. These include thyroid procedures involving only the neck (Spear[32]), hernia (Butsch[2]), gallbladder (Butsch[2]) and sinus operations (Evans[10]). Recently Dressler[9] has drawn attention to the similarities between the post-commissurotomy syndrome and idiopathic pericarditis. He postulates that this type pericarditis may be due to rheumatic involvement of the pericardium. Acute pericarditis, it is well recognized (McKusick and Harvey[21]), may also occur in the course of acute infections by pyogenic organisms, the tubercle bacillus, and protozoal and mycotic organisms; in various connective tissue disorders; in certain metabolic and in neoplastic diseases; in myocardial infarction; and due to trauma. In most such instances, the presence of the primary etiologic process will be readily apparent, although at times difficulties in diagnosis will arise when the pericarditis is the primary or initial manifestation of the disease process. This occasionally may occur, especially in the connective tissue disorders.

The cardinal clinical features of pericarditis include anterior chest pain, accentuated by inspiration, cough and bodily movement, and either a pericardial friction rub or characteristic electrocardiographic findings or both. The electrocardiographic features of acute and subacute pericarditis have been described in detail (Logue and Wendkos[19], Myers[24]), and have been demonstrated to be due to subepicardial myocarditis. The present case shows these in typical form.

Infectious mononucleosis is likewise a common illness, the etiologic agent of which has not yet been identified. Presumably it is an infection due to one or more closely related viruses. Also, there is no specific test for infectious mononucleosis. The heterophil antibody agglutination, though positive in the majority of cases at some time during the illness (Leibowitz[17a]), is nevertheless a nonspecific test. Pathological studies have revealed that in the more severe forms of mononucleosis lymphocytic and mononuclear cell infiltration may be found in all organs of the body (Custer and Smith[7]). The chief clinical features of mononucleosis include a septic fever of intermittent type lasting for several days to 2 or 3 weeks, lymphocytosis with abnormal lymphocytes in the peripheral blood, painful lymphadenopathy and pharyngitis, and splenomegaly. In recent years it has become recognized that this disease may affect most of the organs of the body (Smith[30]). Neurological com-

plications include: serous meningitis, encephalitis, meningoencephalitis, acute polyneuritis, and peripheral neuropathy. Other complications include: rupture of the spleen, spontaneous or nearly so; hepatitis; hemolytic anemia; thrombocytopenic purpura; various pulmonary and cardiac manifestations; acute mesenteric adenitis; abnormal urinary findings; and certain ocular and skin lesions.

The matter of cardiac involvement in infectious mononucleosis has been extensively studied (Jaffe, Field and Master[15], Leibowitz[17b], Wechsler, Rosenblum and Sills[34]). Significant clinical involvement is apparently quite rare. Electrocardiographic abnormalities attributable to the illness may be found, however, in a considerable percentage. These findings consist usually of abnormal T waves in various leads or prolongation of the P–R interval, or both. Second degree block has been found temporarily in two instances. Extrasystoles and nodal rhythm have also been noted.

Clinical or electrocardiographic evidence of pericarditis in infectious mononucleosis occurs only rarely. Evans and Graybiel[11] reported 4 cases which, on the basis of prolonged low voltage or slight inversion of T waves, indicated what they thought to be electrocardiographic evidence of pericarditis. One of these 4 had radiographic enlargement of the cardiac silhouette during the course of the disease. In another, a rub was noted, apparently without pericardial or cardiac symptoms. A fifth case presented as acute pericarditis with effusion, and had an elevated heterophil titer with lymphocytosis, though the usual clinical signs of infectious mononucleosis were lacking. In addition to these 5 cases, in 2 of which the evidence for pericarditis does not appear conclusive, and in one of which the clinical picture of infectious mononucleosis was not described, 9 other conclusive cases of acute pericarditis associated with infectious mononucleosis have been reported Célice *et al.*[4], de Fazio and Marsico[8], Kramer[16], Miller, Uricchio and Phillips[22], Roseman and Barry[27], Shugoll[29] Soloff and Zatuchni[31]). Two of these reports have appeared within the last 6 months (Roseman and Barry[27], Shugoll[29]).

Analysis of these cases reveals an age range from 17 to 42 years. The present one is only the fifth case reported in which pericarditis was the initial manifestation of the disease. In 2 of the 3 cases of Miller *et al.*[22] the pericarditis preceded development of clinical infectious mononucleosis by 1½ and 3 weeks, in the case of Roseman and Barry[27] it preceded it by one week, and in the case of Shugoll[29] by 5 days. Pain appears to have been a prominent feature in all but 2 or 3 of these cases. A pericardial friction rub was heard in 6 or 7 of the total cases, or about one-half. Transient enlargement of the cardiac silhouette was present at some time in 6 instances. Serial electrocardiographic changes typical of, or compatible with, pericarditis are described in all case reports. In a number of instances, however, the acute electrocardiographic phase of S–T segment elevation was not observed.

Summary. A case of acute pericarditis followed 10 days later by clinical infectious mononucleosis has been presented. The pericarditis was characteristic clinically of the acute idiopathic type. Acute pericarditis is felt to be one of the varied manifestations of infectious mononucleosis, and this variety of pericarditis should not, strictly speaking, be included in the idiopathic category. With the increasing precision in diagnosis of virus diseases by serologic and isolation methods presently being gradually realized, it seems likely that more and more cases of acute benign pericarditis will be separated from the idiopathic group.

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SUMMARIO IN INTERLINGUA

Pericarditis Acute Como Manifestation Initial De Mononucleosis Infectiose

Es presentate un caso de pericarditis acute, sequite 10 dies plus tarde per clinic mononucleosis infectiose. Le pericarditis, in su manifestationes clinic, esseva characteristic del typo idiopathic acute. Es opinate que pericarditis acute es un del variate manifestationes de mononucleosis infectiose, e iste varietate de pericarditis non deberea—a strictemente parlar—esser includite in le categoria idiopathic. Viste le crescente precision diagnostic in morbos virusal, que es currentemente e gradualmente effectuate per methodos serologic e isolational, il pare probabile que plus e plus casos de acute pericarditis benigne va esser separate ab le gruppo idiopathic.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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ANIMAL VIRUSES TRANSMISSIBLE TO MAN

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VIRUSES would appear to possess certain characteristics which make them of special interest when transference of infection from one animal host to another is involved. The fact that they propagate within cells and are so intimately related to the cell's physiology would seem to set them apart. Perhaps because propagation takes place within the cell, adaptation is a marked characteristic. A changed capacity to invade a new host is associated with a new disease-producing role. This would appear to be important if one considers viruses that are normally pathogenic in animals but occasionally may be invasive for man. It emphasizes, too, that no virus found in animals whether a disease producer or one in biological balance should be considered unable to become a pathogen for man.

The possible variation in properties because of periodic environmental changes produces a new population of viral particles which possess characteristics at variance with those ordinarily found in the original host. Upon this factor are based several of the most efficient immunizing agents.

The reason for emphasizing these points is to indicate that any relationship between viruses found in lower animals and man must not be considered static. Rather, because biological changes are constantly taking place, there can be no fixed relationship.

Obviously, within the confines of this paper, consideration cannot be given to viral agents of all animals nor all viral agents of each animal. Therefore this article will deal only with a limited number of conditions found in domestic animals and birds. It may

be advantageous to enumerate in tabulated form the conditions, also the animals and birds to be considered.

VIRUSES THAT MAY BE TRANSFERRED FROM:

HORSE TO MAN;
- Encephalomyelitis (Western Type)
- Encephalomyelitis (Eastern Type)
- Encephalomyelitis (Venezuelan Type)
- Encephalitis (Japanese B.)
- Encephalitis (St. Louis)
- Infectious Anemia

COW TO MAN;
- Vesicular Stomatitis
- Foot and Mouth Disease
- Cow Pox

SHEEP TO MAN;
- Louping Ill

DOG TO MAN;
- Rabies

CAT TO MAN;
- Cat Scratch Fever

FOWL TO MAN;
- Newcastle disease
- Ornithosis (Psittacosis)

VIRAL AGENTS OF HORSES PATHOGENIC FOR MAN. It is unlikely that the viral agents of horses known to cause infection in man form a complete list. Several agents are not native to the horse but affect him as an accidental bystander in a manner similar to that in which man is affected. However when epizootics are in progress the horse may be a supplementary but transient reservoir of virus from which man received an infective agent. The majority of these agents are arthropod borne and this may determine the narrow geographic limits within which are found certain conditions.

EQUINE ENCEPHALOMYELITIS. Clinical histories seem to indicate that this disease has been present from time to time in horses in North America. It was not until 1930, however, when Meyer, Haring and Howitt[17] isolated a specific virus, that light was thrown on the nature of the causative agent. This was soon followed by the demonstration by Ten Broeck and Merrill[22] that the agent found in horses in the Atlantic States differed serologically from that found in the West. Although the two agents produce a similar clinical condition they are nevertheless of different serotypes. Still another serotype was added later when in 1939 Kubes and Rios[15] in Venezuela isolated a virus which produced a clinical disease of horses similar to that produced by the Western and Eastern types. Each of these in general has been confined to a geographic region. Each of these types was shown capable of invading and producing encephalitis in man[10,12,25], this being confirmed on many occasions.

Two factors would appear to be of especial interest. That the different types of virus are confined within rather definite although extensive geographical limits seems certain. This has opened a field for extensive investigation that has yet to throw light on the question. It would seem that unknown biological reservoirs are necessary to maintain the infective agent from year to year. Neither the horse nor man is a reservoir because the virus disappears from the blood within a few days. Therefore it is likely that some other form or forms of life are required in which a biological balance can be achieved. It may well be that different types require different biological reservoirs and this in turn determines the geographic distribution. It has been demonstrated that some mosquitoes may carry the infection but

evidence suggesting that vectors carry the virus over from one season to another is lacking. Information on this whole broad field is exceedingly spotty and not sufficiently complete to form a pattern.

An interesting point touching this field is the number of inapparent infections. Following the 1941 outbreak in Western Canada, Mitchell and Pullin[18] made a survey of human sera using the presence of neutralizing antibody as a criterion of past infection. Sera was only accepted when taken from individuals having no history of clinical infection. The results indicated that almost 19% of the sera from persons in Manitoba showed neutralizing antibody. As a control, sera were obtained from persons in Ontario and Quebec. Two persons in Ontario showed neutralizing antibody of whom one had come from the West and the other lived on the border of Manitoba. No serum possessing neutralizing antibody was found in Quebec. This appears to indicate a sharp demarcation line resulting either from the reservoir source of virus or the presence of an appropriate vector. There was also an unexpected number of persons who had been infected.

St. Louis Virus Encephalitis. In 1933 an epidemic of encephalitis occurred among persons in the St. Louis area. From material taken from an infected individual Webster and Fite[24], also MacKenfuss, Armstrong and Webster[16], isolated a virus that possessed distinct properties. Again the native reservoir is unknown. However, in 1941 Cox, Philip and Kilpatrick[7] showed that horses are susceptible to the virus. A year later, Hammon, Carle and Izumi[11] confirmed this. It is unlikely that the horse is the native carrier of the virus although under certain conditions he may be a temporary reservoir.

There are several other viruses having similar properties. These include Japanese B isolated in 1935[21], Russian Spring-Summer isolated in 1938, and California virus isolated in 1952. What biological relationship, if any, they have with the horse has not been determined but it seems unlikely that he plays a conspicuous role.

A number of the viruses mentioned have a serological relationship determinable by the complement fixation or virus neutralization test. As an example Western and Eastern equine viruses are slightly related to each other but not to the Venezuelan type. There is also some antigenic relationship between St. Louis, Russian Spring-Summer and California viruses.

The fact that certain arthropods may act as vectors in the laboratory and that virus has been found in them in some instances under field conditions would seem to indicate that they supply the vital connecting link between the source of virus and the victim. However, much research remains to be done in this field before firm opinions can be formed.

A problem of equal or more importance is related to the continuing reservoirs of virus. Work already done suggests that birds may play this role. But again the field requires much more extensive work before a sufficiency of evidence can be accumulated.

Equine Infectious Anemia. A most remarkable viral condition of horses is widely distributed. The virus possesses some unusual characteristics. Affected animals may die from an acute attack lasting only a few days or they may appear to recover slowly although they remain carriers for life. There are a few instances of human infection, the case of Luhrs being a classical example. Luhrs was the head of the Veterinary Service of the Imperial German Army[13]. He accidentally pricked his finger with a needle contaminated with the virus.

He became infected and was quite ill for several months. Virus could be recovered from his blood for at least 3 years.

However, the number of instances of this kind is extremely small and the infection in man is but a rare phenomenon.

CATTLE TO MAN. *Vesicular Stomatitis.* The virus producing this infection in cattle is equally invasive for the horse. It has a wide geographic distribution and although the resultant disease was seen from time to time it remained unrecorded until 1901 when Theiler[23] of South Africa recognized it as a separate entity. It was not until 1926, however, that the specific virus was isolated. At this time Cotton demonstrated a virus in an outbreak. The following year he showed there are two serotypes[6]. Before the virus was discovered it was noted that the disease might be transferred to man[5]. An influenza-like condition is produced with ulcers on the buccal mucosa and lower lips.

Persons employed in research institutions such as Plum Island, U.S.A., where vesicular disease is under intensive study are likely to experience inapparent or more marked infection.

Foot and Mouth Disease. This virus infection is of interest, since it was the first viral agent discovered in the animal kingdom and it is the most contagious of all animal infections encountered.

The virus affects ruminants and swine. Man has been invaded occasionally. Fortunately the disease has been present in North America only rarely. Although reported in man the number of infections are so rare that the disease in him can be ignored. It is possible too that some of the reported cases were vesicular stomatitis, a condition more easily transferred.

Cow Pox. Historically this disease holds a place of importance out of all proportion to its effects on man. The verification by Jenner of the rural belief that an attack of cow pox protects against small pox led to closing the door on the tragic past and to a new age of security for mankind. The fact that cow pox virus produces only a mildly pathogenic process in cattle and man and that the causative virus is related antigenically to variola virus are the two factors that have led to the remarkable importance of vaccinia in the history of mankind.

Cow pox virus produces a condition characterized by lesions on the teats and sometimes on the mammary glands of cows. However, there is evidence of another agent[5] that produces a similar condition in cattle and gives rise to milkers nodules. This is marked by nonpustular lesions surrounded for a few days by an erythematous rash. Much work remains to be done before the relationship of what appears to be two conditions can be precisely understood.

An interesting feature of changed biological relationships is that before the days of vaccination, persons coming in contact with the mammary glands of cattle were from time to time infected with cow pox. Now the relationship is reversed. With the extensive employment of vaccination few persons are susceptible but cattle may be infected from individuals who have been recently vaccinated.

Q Fever. Although the causative agent of this condition is closely associated with the Rickettsial group, it nevertheless possesses properties that suggest inclusion in the viruses.

The disease was first noted in Australia among abattoir workers and was studied by Burnet[4] and other members of the Queensland Health Department who demonstrated the causative

agent. Since then it has been found in many parts of the world.

In Australia the agent appears to have a reservoir in one of the marsupials and from this is carried by vectors to animals and man. In the United States and Europe ruminants are the chief reservoirs. Cattle are doubtless the great distributors of the causative agent because they also carry the agent in the mammary gland and man may be infected from milk aerosols or from other contamination.

An interesting feature is the number of laboratory infections. Almost every laboratory that has worked extensively with the causative agent has had infected personnel. There is evidence to indicate not only that it may invade through the respiratory route but that an extremely small number of organisms are required.

PIG TO MAN. Vesicular stomatitis and foot and mouth disease are both found in pigs. These have been dealt with already and require no further attention. Pigs are also the reservoir of the causative virus of pseudo-rabies (Aujeszky's disease). The rather wide host range of this virus suggests that an open mind should be kept regarding its potential capacity to invade man.

SHEEP TO MAN. The viruses of which sheep are the principal host are unimportant from the standpoint of human disease. One is worthy of mention because of its serological properties.

Louping Ill. This infection bears a Scotch name, leaping ill. This refers to the spasmodic movement of infected sheep. Its importance lies in the close serological relationship between the causative virus and that of Russian Spring-Summer virus. Because of this more data will have to be collected and further study carried out before the place of this virus as a potential invader of man can be determined.

DISEASES OF DOGS TRANSFERABLE TO MAN. *Rabies.* The causative virus of this condition is capable of invading all warm blooded animals and to a lesser degree, birds. It is the canine species and particularly the dog that form the transmitters of infection. This results from aggressive biting habits and proximity to man. Cold-blooded animals such as frogs appear to be resistant.

Fortunately there is only one type of the causative virus although strains may differ in degree of virulence. There is also evidence to indicate that changes in virulence occur when the virus is passed in serial order in a species. The observation of Pasteur in which he established a fixed virus for the rabbit was the first work in this particular field although its significance was not appreciated for many years.

Because the dog is closely associated with man, it is the presence of rabies in him that has formed the core of the problem for years. Within recent decades another factor has become involved. This in many respects alters the problem.

The presence and spread of rabies in the wild animal population, particularly in foxes and wolves, has added to the difficulties. Canada is a good example. Except for short periods, rabies was unknown in the country. When it occasionally gained entrance the infection was stamped out by a vigorous control of the dog population. Several years ago, tales commenced to come from the north country indicating frequent deaths in the dog population and the occasional peculiar behavior of wild animals. When an investigation was made Plummer[19,20] was able to report the presence of rabies. The infection quickly spread southward and involved many of the settled parts of the country. The dog was only of secondary importance, the principal reservoir of

virus being contained in wild animals, particularly the fox. Some biologists believe that a mutation has occurred in these animals. A few years ago the fox shunned settled districts when possible, but now he has become in part an urban dweller. However this may be, it is at least true that an unexpected number of foxes are found in old settled areas and when rabid they invade towns or even dwellings. The control of the disease in dogs at present may fail to eliminate the infection from a country.

In addition to schemes of elimination, vaccination of exposed persons or potentially exposed animals is a necessity. Anti-rabies vaccines present several interesting features whether viewed from a scientific or historic background. The work of Pasteur demonstrated that the agent of street rabies carried in serial order in rabbits took less and less time to kill. Finally a point was reached when rabbits died in 6 or 7 days. The cords from such rabbits dried over caustic potash for varying lengths of time were found to kill a rabbit approximately in ratio to the time dried. It was assumed that attenuation of the agent had taken place, although it may have represented the number of surviving particles. This is rather suggested by the modifications of the original Pasteur method. The modifications usually were related to the length of dessication. Finally fresh cord, well-diluted, was employed subcutaneously. There were other modifications largely dependent on the addition of a chemical to the ground tissue, the most widely employed being phenol.

In 1948 Koprowski and Cox[14] introduced a product which had its origin in a fine background of basic research. Recognizing that changed virulence for one species often indicates a change in virulence in the opposite direction for another host, they succeeded in propagating a strain of virus in the brain of day-old chicks in serial passage. In this way, the virus was altered in its virulence for mammals while at the same time its antigenicity was maintained. This broadly speaking is the background of live vaccine. The methods used for raising the resistance of man can be employed with suitable modifications in various animals.

In conclusion, it can be said that rabies of dogs is in general the key to human exposure and that the control of the disease in those animals is in large measure possible. The great problem remaining for which there is no evident easy solution is rabies in wild animals.

CATS TO MAN. In addition to infections such as rabies common to several species, there is found a condition in which the cat plays a role.

Cat Scratch Fever. Foshay seems to have been the first to recognize cat scratch fever as a separate disease entity when in 1932 he was investigating tularemia[8]. Hanger and Rose[8] developed a tissue antigen that gave a local reaction after intracutaneous administration. This has since been employed widely and with a considerable degree of success.

The comparatively constant association of cats directly or indirectly with exposure is rather convincing evidence that these animals play an important role. The failure to infect cats and the absence of reaction to the Hanger and Rose antigen has led some to believe that the animals are vectors of a virus obtained elsewhere. It is doubtful if this view is sound. It is possible that the host and the causative agent have struck a delicate biological balance in which no active infection is produced by the colonization of the agent. Monkeys appear to be susceptible and the free employment of these animals to investigate cats that have produced

wounds followed by infection in man might throw light on a problem that is at present far from solved.

FOWL TO MAN. *Newcastle Disease.* A disease associated with a high mortality had been noted in chickens and fowl in several parts of the world. Doyle[9] investigated an outbreak in Newcastle-on-Tyne, England, and from affected individuals obtained a filter-passing virus. This was soon confirmed by many workers. In 1944 Beach[1] demonstrated that a virus which he had isolated from fowl in California showing respiratory and neurological symptoms was in fact the Newcastle disease virus of Doyle. From this time on, the condition has received intensive investigation in many parts of the world.

In 1942 Burnet and Ferry[3] showed that man might be invaded. In him the virus usually produces a conjunctivitis with inflammation of the surrounding structures. Fever and other symptoms of a mild influenzal-like character may occur. Recovery is usually complete in 10 days or 2 weeks.

In addition to the capacity of the virus to invade man, it is of interest because of several properties it shares with the virus of influenza.

Ornithosis (Psittacosis). This condition has likely existed among psittacine birds for centuries in certain areas. Probably in these local areas man has long been affected. Three factors have combined to make the disease important to man; the number of infected birds that are latent carriers, the severity of the disease produced in man, and the demand for the widespread distribution of ornamental birds.

In 1879 a disease in man is said to have been associated with sick parrots. After this many false starts were made in attempts to determine the cause of the condition. Finally in 1930 Bedson and Western[2] demonstrated a virus. Independently but later several other workers reported similar findings. The agent belongs to the psittacosis-lymphogranuloma group. The organism goes through several stages of development. Elementary bodies form the infective stage of the virus.

The disease is extremely dangerous to laboratory workers when birds are employed in experiments. Fortunately the mouse is susceptible and danger from this source is much less because it is evidently in aerosol form that the virus easily passes to man.

The infection in man is severe, the mortality being approximately 18% until the advent of aureomycin therapy.

The gravity of the clinical condition in man and the number of carrier birds showing little or no evidence of infection emphasizes the necessity of a rigid control over the importation of psittacine birds.

Concluding Remarks. In conclusion, it can be said that the subject is extremely extensive and only a few highlights have been touched. If in addition to conditions found in domestic animals, there was taken into account conditions present in other animals, such as monkeys, it becomes evident how extensive is the field.

One point is worth emphasizing, namely that much of the field remains unexplored and great gaps are to be found in present knowledge. There is also the factor that viral agents are not static but may change from time to time and consequently, their potential capacity to produce harmful effects in man alter.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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INTERACTIONS OF NUTRITION AND INFECTION

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THE idea that nutritional deficiencies and infections have something to do with each other follows from the historical association between famine and pestilence. Numerous field and clinical observations and many experimental studies support this view. The extensive literature also includes many conflicting and inconclusive observations, to such extent as to obscure good evidence that many of the important infections of human populations are rendered more serious in their consequences by the presence of malnutrition; that a few infections are indeed less severe when associated with nutritional deficiency; and that many infections themselves precipitate nutritional disturbances.

Definite patterns of interaction between nutrition and infection can be identified. This information is useful in planning health programs for underprivileged areas; it also has value as a stimulus and aid to research.

The bibliography of this review is necessarily and desirably selective. Publications with no direct reference to interaction of nutrition and infection are omitted except where the data bear on some essential feature of one or the other. On some aspects of the problem the number of publications is so great that only representative papers or review articles are cited. Many contributions in the older literature have been disregarded as failing to meet modern scientific criteria; few areas of investigation are more replete with unsupported statements of opinion, impression and speculation.

Soon after World War I the separate

currents of investigation in infectious disease and in nutrition began to meet, a circumstance largely accounting for the time distribution of reports of their interaction. Microbiological research continued to identify new infectious agents, but with growing appreciation that constitutional factors determining host resistance had to be studied along with antibodies in measuring the reaction of the host to invasion. Concurrently, increasing numbers of specific nutrients were recognized and the scientific basis of nutrition was established by biochemical and field studies. These nutrients proved so beneficial that it was natural to associate them with the long standing notion that nutrition and infection are interrelated, and to imply that their presence was protective. The oversimplication implicit in such terms as the "anti-infective vitamin" for vitamin A, diligently fostered by vitamin salesmen, carried medical practice far beyond scientific evidence.

During and after the second World War excessive claims of the value of vitamins in preventing and treating infections, abuses in vitamin administration, and the lack of result when these elements were added to an already adequate diet led to a sharp reaction against vitamins and against nutrition in general, as factors in resistance to infection. Moreover, a number of experimental nutritional deficiencies were found to retard the development of viral and protozoal infections through adverse effect on the metabolism of the infectious agent. In this context, the review of Aycock and Lutman[17] rejected vitamin prophylaxis of infection as a general epidemiological principle.

The reports of conferences in 1949[65], and in 1955[230] seemed to indicate that the relationship of each nutrient to each infectious agent in each host would need to be worked out individually, an approach supported by the recent reviews of Geiman[114], Smith[307] and others[55,295c]. However, even in 1949, Howie[149] recognized a greater uniformity among results of different workers than a casual familiarity with the literature would suggest. McClung[207] stressed the frequency with which nutritional deficiency lowers resistance to bacterial infections in experimental animals, and Cannon[50e] insisted that at least minimal dietary protein is necessary for immunological defense against infection. Schneider[295a, 295e] helped maintain perspective in stating that his negative results with identified virulent or avirulent strains of an infectious agent, tested in genetically homogenous mice having a specific nutritional deficiency, were of less practical significance than his positive results with strains of ordinary virulence in randomly bred mouse populations.

Two useful reviews summarize the older literature. Clausen[67a] suggested that although diet does not as a rule influence frequency of infections, severity may be greatly enhanced by an inadequate diet, a generalization still valid. In reviewing over 300 reports concerned only with the effects of vitamins, Robertson[271] stressed the frequency with which experimental deficiencies of vitamins A and C lowered resistance to bacterial infection.

Terms and Interpretations. In the interests of clarity we have spoken only of an increase or decrease in resistance to infection, avoiding the term susceptibility. These are reciprocal functions; as one increases the other decreases. Schneider[295f] distinguished "susceptibility factors" which decrease the extent or effect of infections when withheld, from "resistance factors" which lead to their increase when not supplied. We find it more convenient to express this difference by the term

"antagonism" for that situation where a nutritional deficiency results in decreased frequency or severity of an infection, and to use "synergism" where deficiency results in an increase. These terms imply an interaction of host and infectious agent in determining the outcome of infection[307,329]; in general, synergism is the usual result when the dominant action of the nutritional deficiency is on the host, and antagonism when the main impact is on the infectious agent.

A difference also is to be recognized between two broad forms of malnutrition. A reduction in intake of all essential nutrients leads to a state of undernutrition or inanition called marasmus in children. The other situation is that of a relative or absolute deficiency of one or more specific nutrients. The distinction is important because the former may not be associated with detectable physiological or biochemical changes, while signs of specific nutritional deficiencies develop as a result of disproportion among nutrients. The many biochemical changes in kwashiorkor and their absence in infantile marasmus[29,153], or the development of beriberi only when the intake of calories is relatively greater than of thiamine, are examples.

In some experiments the low palatability of the diet or complications of induced specific deficiences such as anorexia, vomiting or diarrhea have led to material differences in food intake between control and experimental animals. Interpretation is then hazardous, since positive results may be due to food restriction alone. Such experiments do not measure the specific deficiency intended.

Further confusion results from failure to recognize that nutrition influences infection in at least four ways, and that negative evidence about one mechanism does not apply to all. Nutritional deficiencies conceivably determine the progress of infection either through action on the host to facilitate initial invasion of the infectious agent; through an effect on the agent once established in tissues; through favoring secondary infection, of especial importance under field conditions; or by retarding convalescence after infection.

Many of the better controlled experimental studies have measured resistance almost exclusively by ability of the host to produce antibodies. Antibody response to experimental or natural infection is not synonymous with resistance, a term defined in the American Public Health Association Handbook, Control of Communicable Diseases in Man as "the sum total of body mechanisms which interpose barriers to the progress of invasion of infectious agents"; this includes both specific antibodies and nonspecific (autarcetic) mechanisms.

Patterns of Interaction. An imposing number of publications deal with the association of nutritional deficiency and infection in the human or animal host. Each study has been classed arbitrarily as evidencing synergism, antagonism or no demonstrable effect. This information, along with the particular host, the infectious agent concerned and the nature of the nutritional deficiency, is presented in a series of tables arranged according to major divisions of infectious agents.

From the assembled data, a number of patterns of behavior become evident; they are identified and briefly described. The responsible mechanisms are the major concern in subsequent discussion, along with practical implications for prevention and control.

Bacterial Infections. Interactions between dietary deficiencies and bacterial infections are regularly, indeed almost uniformly synergistic, Table 1.

TABLE 1.—EFFECT OF NUTRITIONAL DEFICIENCIES ON BACTERIAL INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Guinea pig	Multiple (green food)	Pneumonia	Synergistic	Smith, 1913[313]
Human	General	Tuberculosis	Synergistic	Faber, 1938[96] Leitch, 1945[183] Leyton, 1946[184]
Mouse	Acute starvation 75% undernutrition	Tuberculosis	Synergistic No effect	Dubos 1947, 1948[87a,b]
Rat	50% caloric undernutrition Vitamin A	Tuberculosis	No effect	Sriramachari and Gopalan, 1958[317]
Mouse	Multiple	Salmonella and 4 other bacteria	Synergistic	Webster, 1930[356]
Mouse	Multiple (? Protein)	Salmonella	Synergistic	Watson, Wilson and Topley, 1938[353]
Pigeon	Starvation (4 days)	Anthrax	Synergistic	Corda, 1923[73]
Mouse	Fasting	*Shigella flexneri III*	Synergistic	McGuire *et al.* 1958[214]
Human	Multiple	Respiratory infections Tuberculosis	Synergistic	Orr and Gilkes, 1931[240]
Rat	Vegetarian diet	cholera	Synergistic	Chen and Li, 1930[58]
Rat	Vegetarian diet	Pneumococci	No effect	Chen and Li, 1930[58]
Mouse	Multiple diet	Tuberculosis	Synergistic	Dubos and Pierce, 1947, 1948[88a,b]
Human	Vitamins A and C	Tuberculosis	Synergistic	Getz *et al.*, 1951[117]
Monkey	Vitamins A,C,B and Protein	Bacillary Dysentery	Synergistic	Rao, 1942[259]
Guinea pig	Multiple (green foods)	*Pasturella pseudotuberculosis*	Synergistic	Zachorowski, 1952[374]
Mouse and Rat	Unknown factor in wheat	Pneumococci	Antagonistic	Hitchings and Falco, 1946;[148a,b] Dworetsky, 1949[92]
Mouse	Unknown factor in wheat	Salmonella	Synergistic	Schneider and Webster, 1945[296] Schneider, 1949, 1951[296b,296c]
Rat	Vitamin A	Spontaneous infections (Pneumonia, mastoiditis, sinusitis, ophthalmia, nephritis, pancarditis, cystitis, enteritis, etc.)	Synergistic	McCollum, 1917[209] Drummond, 1919[86] Daniels *et al.*, 1923[78] McCarrison, 1931[206d] Green and Mellanby, 1930[123b]
Infant	Vitamin A	Severe infections	Synergistic	Clausen, 1935[67b] Bloch, 1924, 1928[39a,b]
Infant	Vitamin A	Severe infections	Synergistic	Blackfan and Wolbach, 1933[37]
Rat	Vitamin A	Salmonella	Synergistic	Webster and Pritchett, 1924[357] Pritchett, 1927[251] Lassen, 1930, 1931[178a,b] McClung and Winters, 1932[208b] Seidmon and Arnold, 1932[301] Kligler *et al.*, 1945[165] Robertson and Tisdall, 1939[274]

TABLE 1 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Mouse	Vitamin A	Tuberculosis	Synergistic	Finkelstein, 1931–32[100]
Dog	Vitamin A	Spirochetes (black-tongue of Underhill's syndrome)	Synergistic	Smith *et al.*, 1937[309]
Guinea pig	Vitamin A	Diphtheria toxin Tetanus toxin	No effect	Torrance, 1936[338]
Rat	Vitamins A and D	Tetanus toxin Dead Typhoid Bacilli	Synergistic	Blackberg, 1928[36]
Sheep	Vitamins A and D and minerals	Toxin of lamb dysentery	Synergistic	Mackie *et al.*, 1932[197]
Rat	Vitamin A	Saprophytic bacteria	Synergistic	Boynton and Bradford, 1931[43] Turner *et al.*, 1930[341]
Rat	Vitamin D	Saprophytic bacteria I-P	No effect	Boynton and Bradford, 1931[43]
Mouse	Vitamin D	Pasturella	No effect	Hill, Greenwood and Topley, 1930[143]
Rat	Vitamin D	Pyogenic bacteria	No effect	Green and Mellanby, 1928[123a]
Rat	Vitamin D (subclinical)	Salmonella	Synergistic	McClung and Winters, 1932[208b]
Rat	Vitamin D	Salmonella	Synergistic	Robertson and Ross, 1930[273]
Monkey	Vitamins A and B	Septicemia	Synergistic	McCarrison, 1919[206c]
Bird	Vitamin B	Salmonella	Synergistic	McCarrison, 1918[206a]
Monkey	Chronic folic acid	Dysentery (? Shigella)	Synergistic	Waisman and Elvehjem, 1943[349]
Mouse	Thiamine	Shigella	Synergistic	Sporn *et al*, 1950[315]
Mouse	Riboflavin Pyridoxine Niacin Biotin Folic acid	Shigella	No effect	Sporn *et al.*, 1950[315]
Mouse	Riboflavin Biotin	Salmonella	Synergistic	Kligler *et al.*, 1944, 1946[164,166]
Rat and mouse	Thiamine			Guggenheim and Buechler, 1946[127a]
Rat	Thiamine	Borrelia	Synergistic	Guggenheim and Halevi, 1952[129]
Mouse	Thiamine Riboflavin	Pneumococcus	Synergistic	Wooley and Sebrell, 1942[371]
Rat	Pantothenate	Corynebacterium	Synergistic	Seronde *et al.*, 1956[304]
Rat	Pantothenate Riboflavin	Pneumococcus	No effect	Robinson and Siegel, 1944[275]
Rat	Thiamine Pyridoxine	Pneumococcus	Slightly synergistic	Robinson and Siegel, 1944[275]
Rat and Mouse	Pantothenate	Pneumococcus	No effect	Day and McClung, 1945[80]
Monkey	B Complex	Streptococcus Group C	Synergistic	Saslaw *et al.*, 1943[292]

TABLE 1 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Dog	B Complex	*Clostridium welchii*	Synergistic	Rose, 1928[280]
Dog	B Complex	*S. aureus*	Synergistic	Rose and Rose, 1936[281]
Pigeon	B Complex	Pneumococcus Meningococcus *E. coli* Salmonella	Synergistic (only with low body temp.)	Findlay, 1923[98a]
Pig	B Complex	Salmonella	Synergistic	Luecke, 1955[192]
Rat	B Complex Thiamine	Rat leprosy	Synergistic	Lamb, 1935[173] Badger *et al.*, 1940[19]
Dog	B Complex	Spirochetes (Goldberger Syndrome)	Synergistic	Smith *et al.*, 1937[3, 9]
Human	Riboflavin	Secondary infections of mouth	Synergistic	Riddle *et al.*, 1940[257]
Guinea pig	Vitamin C	Pneumococci Streptococci	Synergistic if advanced scurvy	Schmidt-Weyland and Koltzsch, 1928[294] Jackson and Moody, 1916[151]
Monkey	Vitamin C	*Spirillum sputigenum*	Synergistic	Kelly, 1944[160]
Guinea pig	Vitamin C	Diphtheria bacilli	Synergistic	Wamoscher, 1927[350]
Human	Vitamin C	Pneumococci	Synergistic	Hess, 1932[141b]
Guinea pig	Vitamin C	Diphtheria toxin	Synergistic	King and Menten, 1935[162] Bieling, 1925[34]
Chicken	Vitamin C or other antioxidant	Salmonella	Synergistic	Hill and Garren, 1955[142]
Guinea pig	Vitamin C	Tuberculosis	Synergistic	McConkey and Smith, 1933[210] Birkhaug, 1939[35] Gangadharam and Sirsi, 1953[112]
Mouse	Protein	Salmonella	Synergistic	Watson, 1937[352] Watson *et al.*, 1938[353] Guggenheim and Buechler, 1947, 1948[127c,d]
Mouse	Casein	Salmonella	Synergistic	Miles, 1951[227] Robertson and Doyle, 1936[272]
Rat	Protein	Salmonella (light infection) Tuberculosis (light infection)	No effect on antibodies or blood cells	Metcoff *et al.*, 1948[222] Metcoff *et al.*, 1949[223]
Mouse	Protein	Pneumococcus	Synergistic	Sako, 1942[289]
Rat and Rabbit	Protein	Pneumococcus	Synergistic	Wissler, 1947[366a,b]
Rat	Protein	Spirochetes of relapsing fever	Synergistic	Guggenheim *et al.*, 1951[128]
Mouse	Protein	Staphylococcus *Mycobacterium fortuitum* *M. tuberculosis*	Synergistic	Schaedler and Dubos, 1956[293] Dubos and Schaedler, 1956[89]

TABLE 1 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Chicken	Protein	Pneumococcus	Synergistic	Steffee, 1950[319]
Chicken	Excess fish meal Low fish meal	Salmonella Salmonella	Synergistic Antagonistic	Smith and Chubb, 1957[311] Smith and Chubb, 1957[311]
Rat and Hamster	Vitamin E	Human leprosy	Synergistic	Mason and Bergel, 1955[203]
Rat	Protein	Tuberculosis	Synergistic	Koerner *et al.*, 1949[169]
Rat	Protein	Tuberculosis	No effect	Lange and Simmonds, 1923[175]
Rat	Protein (casein)	Inhalation tuberculosis	Antagonistic	Ratcliffe, 1951[263a]
Hamster	Protein (casein)	Inhalation tuberculosis	Synergistic	Ratcliffe and Merrick, 1957[264]
Guinea pig	Protein (casein)	Inhalation tuberculosis	Synergistic	Ratcliffe, 1954[263b]
Human	Animal protein	Tuberculosis	Synergistic	Marche and Gounelle, 1950[201]
Mouse	Animal protein	Tuberculosis	Synergistic	Sengupta and Howie, 1948–49[303]
Mouse	Fatty acids plus protein	Tuberculosis	Synergistic	Hedgecock, 1955, 1958[137a,b]
Mouse	Starvation	Staphylococcus	Synergistic	Smith and Dubos, 1956[312]

Food restriction leading to starvation or inanition lowers resistance to some bacterial infections. Suggestive early reports[34,271] are confirmed by such well controlled experiments as those of Dubos and coworkers[87a,87b,89,90] who showed that 24 to 48 hours of complete fasting decreased the resistance of mice to staphylococcus, Friedlander bacillus and the tubercle bacillus. With adequate refeeding, normal resistance returned in 1 to 3 days. Substitution of an inadequate diet temporarily aggravated the condition, but eventually these animals also regained normal resistance.

Multiple deficiencies are more common in humans than deficiencies of a single nutrient and therefore are of greater public health significance. Monkeys on a basic rice diet deficient in vitamins A, B, C and animal protein, as observed by Rao[259], had chronic diarrhea typical of bacillary dysentery. McKenzie[217] reported similar findings in East African laborers.

Children and experimental animals on vitamin A deficient diets frequently develop spontaneous infections[67b,123b]. Synergism between salmonella infections and vitamin A deficiency in mice and rats is reported repeatedly, with resistance lowered before clinical signs of deficiency disease. Clausen[67a] and Watson[352] concluded that in most studies vitamin D deficiency was incidental to more important vitamin A deficiencies. Robertson and Ross[273], however, showed significant improvement in resistance by nothing more than ultraviolet irradiation of a deficient diet.

Deficiency of various B vitamins is reported to lower resistance to a variety of infections, particularly intestinal pathogens[166], pneumococci[371], other

Gram-positive cocci[292], spirochetes[309], clostridia[280], and the bacillus of rat leprosy[19]. The frequent and extravagant claims[211a,211b] of a therapeutic effect of vitamin C overshadow all research on this vitamin. Reasonably well controlled studies indicate, however, that severe scurvy reduces the resistance of guinea pigs to Gram-positive cocci[294] and the diphtheria toxin[162].

Difficulty in producing single nutrient deficiencies often confuses judgment as to which of several missing elements is responsible for an observed clinical condition. Guggenheim and Buechler[127c,127d] showed by paired feeding experiments that synergistic effects with salmonella infections and diets intended to be vitamin A deficient were actually better explained by coexistent lowered food intake and probable protein deficiency. The report of Webster and Pritchett[357] that fats containing vitamin A restored resistance to salmonella in colonies of mice on deficient diets was discounted by Watson's[352] demonstration of even more dramatic reaction in mice on similar diets when casein was given. Of particular value methodologically was the application of techniques of experimental epidemiology by Watson, Wilson and Topley[353]. It is usually stated that Metcoff *et al.* failed to confirm a relationship between protein deficiency and resistance to salmonellosis[222] and tuberculosis[223] in rats. Unwarranted extrapolations have been made from the limited objectives of these two carefully designed and executed studies in which the immunologic and hematologic response of animals with minimal, nonfatal infections remained unmodified by deficiencies of short duration. All other studies indicate a more or less proportional loss of resistance with severe protein depletion.

Tuberculosis illustrates better than any other disease the dominant synergistic effect of associated bacterial infection and dietary deficiency. The general increase in tuberculosis during wartime is difficult to ascribe to any single nutritional factor. Faber[95] reported that mortality from tuberculosis in Denmark declined sharply during the final years of World War I after reaching a maximum in 1917, while rates in other European countries continued to rise until the war ended. Although general living conditions deteriorated in Denmark, nutrition improved because export of meat and dairy products ceased with blockade of ports by German submarines. Corroboration comes from prisoner-of-war camps in Germany during World War II. Prevalence of tuberculosis[184] among Russian prisoners was 19%, among the British 1.2%, with marked differences in diet a distinguishing feature. That deficiency of vitamin A and C may lower resistance to tuberculosis is suggested by field studies by Downes[85] in New York and Getz *et al.*[117] in Philadelphia.

A complex dietary interaction of proteins and fats is suggested in tuberculosis by the well controlled laboratory studies of Hedgecock[137a,137b]. When lard was the only source of fat in diets of mice, no protein deficiency effect on resistance could be demonstrated. With a special mixture of five fatty acids from coconut oil, however, addition of protein gave statistically significant protection.

Viral Infections. Antagonism is the common and well defined reaction in virus infections associated with nutritional disorders. Synergism is less frequent. Experiments on virus infections, being generally of more recent date than those with bacteria, have the advantage of modern standards of experimental design and statistical appraisal. Those listed in Table 2 have more reliability.

TABLE 2.—EFFECT OF NUTRITIONAL DEFICIENCIES ON VIRAL INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Chicken	Multiple	Rous sarcoma virus	Antagonistic	Rous, 1911[282]
Mouse	Multiple	Rous sarcoma virus	Antagonistic	Tannenbaum, 1940[327]
Guinea pig	Multiple	Foot and mouth disease	Antagonistic	Olitsky *et al.*, 1928[238]
Rabbit	Multiple	Vaccinia	Antagonistic	Rivers, 1939[269] Sprunt, 1942[316]
Bird	Multiple	Psittacosis	Synergistic	Meyer, 1942[226]
African negro	Multiple	Hepatitis	Synergistic	Findlay, 1948[98b] Hahn and Bugher, 1954[131]
Monkey, Mouse	Multiple	Yellow fever	Synergistic	Kuczynski, 1937[172]
Monkey	Multiple Vitamin B complex	Influenza	Synergistic	Saslow *et al.*, 1942[292]
Monkey	Folic acid	Influenza	Synergistic	Wilson *et al.*, 1947[364]
Cotton rat	Partial inanition Vitamin B	Poliomyelitis	No effect	Weaver, 1945[355a]
Cotton rat	Vitamin A	Poliomyelitis	Synergistic	Weaver, 1946[355b]
Rat	Vitamin D	Coryza	Synergistic	György *et al.*, 1926[130]
Monkey	Thiamine	Poliomyelitis	No effect	Clark *et al.*, 1945[66]
Mouse	Thiamine	Poliomyelitis Theiler	Antagonistic	Rassmussen *et al.*, 1944[261] Toomey *et al.*, 1944[337] Foster *et al.*, 1942, 1944[106a,b,c]
Mouse	Thiamine	Western equine encephalitis	Antagonistic	Kearney *et al.*, 1948[159a]
Chick 1-day old	Thiamine	Avian encephalomyelitis	Synergistic	Cooperman *et al.*, 1946[72]
Chick 2-wk. old	Thiamine	Avian encephalomyelitis	Antagonistic	Cooperman *et al.*, 1946[72]
Pigeon	Thiamine	Psittacosis	Synergistic	Pinkerton and Swank, 1940[248]
Mouse	Pyridoxine (acute)	Pneumonia	Antagonistic	Leftwich and Mirick, 1949[182]
Mouse	Pyridoxine	Pneumonia	Synergistic	Mirick and Leftwich, 1949[231]
Monkey	Pyridoxine analogue (deoxypyridoxine)	Poliomyelitis	Synergistic	Bodian, 1948[41]
Chick embryo Tissue cultures	Thiamine analogue (oxythiamine) Pyridoxine analogue (deoxypyridoxine)	Mumps Influenza	Antagonistic	Cushing *et al.*, 1952[76]
Mouse	Riboflavin	Poliomyelitis	Antagonistic	Rassmussen *et al.*, 1944[262]
Mouse	Riboflavin	Theiler	No effect	Rassmussen, *et al.*, 1944[262]

TABLE 2 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Mouse	Pantothenic acid	Poliomyelitis	No effect	Lichstein *et al.*, 1944[187]
Mouse	Pantothenic acid	Theiler	Antagonistic	Lichstein *et al.*, 1944[187]
Monkey	Folic acid (acute)	Poliomyelitis	No effect	Lichstein *et al.*, 1946[185]
Monkey	Folic acid (chronic)	Poliomyelitis	Antagonistic	Lichstein *et al.*, 1946[185]
Chicken	Folic acid	Rous sarcoma virus	Antagonistic	Little *et al.*, 1948[183]
Mouse	B-complex	Vesicular stomatitis	Synergistic	Sabin and Olitsky, 1938[286]
	Thiamine		(delayed maturation resistance)	Sabin and Duffy, 1940[285]
	Vitamin E			Sabin, 1941[284]
Mouse	Protein deficiency also high protein Low fat	Theiler	No effect	Kearney *et al.*, 1948[159a,b]
Mouse	Choline	Hepatitis(MHV3)	No effect	Ruebner *et al.*, 1958[283]
Mouse, mature	Protein (acute)	Swine influenza	Antagonistic	Sprunt, 1949[316]
	Protein (more than two weeks)	Swine influenza	No effect	Sprunt, 1949[316]
Mouse, immature	Protein	Swine influenza	No effect	Sprunt, 1949[316]
Mouse	Tryptophan	Theiler	Antagonistic	Kearney *et al.*, 1948[159b]
Mouse	Lysine	Poliomyelitis	No effect	Jones *et al.*, 1947[134]
Rat	Protein defic.	Hepatitis (? human)	Synergistic	MacCallum and Miles, 1946[195]
Mouse	Potassium Phosphorus	Theiler	Antagonistic	Lichstein *et al.*, 1946[186]
Mouse	Calcium Sodium Magnesium	Theiler	No effect	Lichstein *et al.*, 1946[186]
Mouse	Potassium	Poliomyelitis	No effect	Jones *et al.*, 1947[134]
Mouse	Phosphorus Calcium	Poliomyelitis	Synergistic	Foster, 1949[105]

Chance laboratory observations indicate that general malnutrition is antagonistic to the viruses of foot and mouth disease[238], Rous sarcoma[282], vaccinia[269, 316] and psittacosis[226]. Clinical studies in Africa[98b,131] on enhanced fatality of infectious hepatitis in malnourished West Africans are supported by clinical observations[345] that adequate protein nutrition limits sequelae of chronic cirrhosis. Only two experimental studies with vitamin A[355b] and D[130] deficiency were encountered, both suggesting synergism.

Most instances of antagonism to viral infections are with members of the vitamin B group. The action of thiamine deficiency in increasing resistance of mice to the viruses of poliomyelitis[106b,261,262] and western equine encephalitis[159a], and of avian encephalomyelitis[72] in chicks seems well established. Lichstein *et al.*[185] found that acute folic acid deficiency had no ef-

fect on poliomyelitis infection in monkeys but that chronic deficiency resulted in high grade resistance. On the other hand increased resistance to pneumonia virus (P.V.M.) of mice has been demonstrated with acute pyridoxine deficiency[182] which changed to synergistic reduction of resistance in chronic deficiency of more than 8 days[231].

Viruses show considerable specificity in their interactions with vitamin deficiencies. Riboflavin deficiency was antagonistic to poliomyelitis infection in mice but had no effect on Theiler virus[262], while pantothenic acid deficiency was antagonistic to Theiler virus and had no effect on poliomyelitis[187]. The evidence is unconvincing that vitamin C has any therapeutic effect on viral infections despite frequent firmly held clinical opinion.

Protein deficiencies ordinarily have little or no effect on viral infections. A striking exception is the report by Kearney *et al.*[159b] that tryptophan deficiency gives almost complete protection of mice from the paralytic effects of Theiler virus, with nearly all control animals paralyzed. Despite lack of paralysis, virus titers in brains of deficient mice were as high as in normally fed controls, and histological evidence of infection equally marked.

The results of deficiency of specific minerals range from synergism to antagonism. For example, phosphorus deficiency was synergistic with poliomyelitis infection in mice[105], but antagonistic to Theiler virus[186]; potassium deficiency had no effect on poliomyelitis[154] and was antagonistic to Theiler virus[186], while calcium deficiency was synergistic with poliomyelitis[105] and without effect on Theiler virus[186].

TABLE 3.—EFFECT OF NUTRITIONAL DEFICIENCIES ON RICKETTSIAL INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Rat	Vitamin A	Typhus	Synergistic	Zinsser *et al.*, 1931[377] Wertman *et al.*, 1952[361]
Rat	Thiamine Pantothenic acid Pyridoxine Riboflavin Folic acid B_{12}	Murine typhus	Synergistic	Wertman and Sarandria, 1951, 1952[362a,b,c] Pinkerton, 1949[246b] Pinkerton and Bessey, 1939[247] Fitzpatrick, 1948[101]
Rat	Vitamin C	Murine typhus	Synergistic	Pinkerton, 1949[246b]
Guinea pig	Vitamin C	Epidemic typhus	Synergistic	Pinkerton, 1949[246b] Zinsser *et al.*, 1931[377]
Rat	Protein	Murine typhus	Synergistic	Fitzpatrick, 1948[101]
Rat	Pyridoxine Nicotinic acid Choline	Murine typhus	No effect	Fitzpatrick, 1948[101]

Rickettsiae. All studies of the interaction of malnutrition with rickettsial infections showed synergism, Table 3. In laboratory studies by Wertman and coworkers[361,362a,362b,362c] almost all members of the vitamin B group except niacin brought about decreased antibody production against murine typhus in rats. Pinkerton[246a,246b] and Pinkerton and Bessey[247] showed that deficiency of ascorbic acid, riboflavin, pantothenic acid, thiamine, vitamin A

and protein is synergistic with murine typhus in rats, and starvation with epidemic typhus in guinea pigs. Epidemics of typhus have been linked with famine more consistently than almost any other disease. Aycock and Lutman[17] and Sigerist[306] developed historically the idea that this relationship is probably secondary and incidental, since war brings both famines and typhus epidemics.

Helminths. With few exceptions the consequences of parasitic infection[150, 339b] are generally more serious in malnourished hosts[114,307], a synergistic reaction, Table 4.

TABLE 4.—EFFECT OF NUTRITIONAL DEFICIENCIES ON HELMINTH INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Dog	Multiple	*Ancylostoma caninum*	Synergistic	Foster and Cort, 1931, 1932, 1935[104a,b,c,d]
Rat	Multiple	*Nippostrongylus muris*	Synergistic	Chandler, 1932[64a]
Lamb	Multiple	*Trichostrongylus axei*	Synergistic	Gibson, 1954[118]
Lamb	Multiple (ewes as well as lambs)	*Trichostrongylus* sp. *Ostertagia* sp. *Haemonilius* sp. *Aesophagostonum* sp. *Cooperia* sp.	Synergistic	White and Cushnie, 1952[363]
Lamb	Multiple	*Haemonchus contortus* sp. *Esophagostonum* sp. *Columbianum* 7 additional species		Laurence *et al.*, 1951[179] Taylor, 1934[331]
Mouse	Partial fasting or alcohol	*Hymenolepis nana*	Synergistic	Larsh, 1947[176a]
Chicken	Vitamin A	*Ascaris galli* *A. lineata*	Synergistic	Ackert *et al.*, 1927[2] Ackert and McIlvaine, 1931[3]
Chicken	Vitamin D	*A. lineata*	No effect	Ackert and Spindler, 1929[5]
Dog	Vitamin A	*Toxicara canis* *Toxoscaris leoninia*	Synergistic	Wright, 1935[372]
Pig	Vitamin A	*A. lumbricoides*	No effect	Clapham, 1934[62c]
Chicken	Vitamin A	*Syngamus trachea*	Synergistic	Clapham, 1934[62d]
Rat	Vitamin A	*Parascaris equorum*	Synergistic	Clapham, 1933[62a]
Chicken	Vitamin A	*Heterakis gallinae*	No effect	Clapham, 1934[62b]
Rat	Vitamins A,D,E and protein	*Hymenolepis dimunata*	No effect	Chandler, 1943[64b]
Rat	Vitamin A	*Strongyloides ratti*	Synergistic	Lawler, 1941[180]
Rat	Vitamin A	*Schistosoma mansoni*	Synergistic	Krakower, 1940[177a]
Rat	Vitamin A	*Trichinella spiralis*	Synergistic	McCoy, 1934[212]
Rat	Vitamin C	*S. mansoni*	No effect	Krakower *et al.*, 1944[176b]
Mouse	Vitamin E, selenium and cystine	*S. mansoni*	Synergistic	DeWitt, 1957[82]

TABLE 4 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Duck	Vitamin B Comp.	*A. galli*	Synergistic (more worms but smaller)	Ackert and Nolf, 1931[4]
Chick	Pteroylglutamic acid	*A. lineata* *A. perspicillum*	Synergistic	Sadun *et al.*, 1949[288] Zimmerman *et al.*, 1926[375]
Rat	Thiamine Riboflavin	*N. muris*	Synergistic	Watt, 1944[354]
Chick	Protein (Arginine, glycine, leucine, lysine)	*A. galli*	Synergistic	Riedel and Ackert, 1951[268b]
Chicken	Protein	*A. lineata*	Synergistic	Ackert and Beach, 1933[1]
Rat	Protein	Trichinella	Synergistic	Rogers, 1942[278d]
Dog	Diet of whole milk only	*A. caninum*	Synergistic	Foster, 1936[103]
Rat	Protein	*N. muris* *H. nana*	Synergistic	Donaldson and Otto, 1946[84] Larsh, 1950[176b]
Rat	Iron (whole milk)	*N. muris*	Synergistic	Porter, 1935[250]
Chicken	Calcium	*H. gallinae*	Synergistic	Clapham, 1934[62b]
Chick	Manganese	Tapeworm	Synergistic	Harwood and Luttermoser, 1938[12]
Chicken	Phosphorus Calcium	*A. galli*	Antagonistic	Gaafar and Ackert, 1953[111]
Chicken	Manganese	*A. galli*	No effect	Gaafar and Ackert, 1953[111]

Nutritional deprivation has long been known to aggravate hookworm infection in human populations. Laboratory confirmation was provided[104a,104b,104c,104d] through dogs infected with *Ancylostoma caninum;* heavy infections of malnourished dogs were followed by prompt loss of worms and reduction in egg production when the animals were placed on an adequate diet. Well nourished dogs are infected with difficulty by the cat strain. and likewise the normally fed cat with the dog strain. On poor diets this "specific resistance" is lost.

Hymenolepis infections of rats and mice were rendered more serious by generalized dietary inadequacy[54a]. When both vitamins A and D were deficient, infection of young rats with adult Trichinella was heavy, large numbers of larvae were deposited in muscle, and active immunity to reinfection was absent[212].

In vitamin B-complex and pteroylglutamic deficient fowl, ascarids[4,288] appear in greater numbers than in controls. Both thiamine and riboflavin deficiencies proved synergistic with infections of Nippostrongylus in rats[354], an effect even more pronounced in superinfection.

Deficiency of protein permits greater development of Ascaris[268b], Trichinella[278d], Nippostrongylus[84] and Hymenolepis[176b] in various animal hosts. In ascaris infection of chickens the quality as well as the quantity of protein is important[268a].

An associated iron deficiency in Nippostrongylus infection in rats[250] and hookworm in man[75] results in increased parasitism, and conversely iron therapy reduces the number of worms; the

iron deficiency produced by hookworms thus leads to still heavier infections. Deficiencies in phosphorus and calcium[111] proved antagonistic to ascaris infection of chickens, suggesting specific dependence on these metabolites; the worms were reduced in number and in size.

Protozoa. Synergism and antagonism are observed with almost equal frequency in protozoan infections, Table 5. Intestinal protozoa, especially amebae, are almost uniformly synergistic with deficiencies, while protozoa of the blood, especially malaria parasites, are more frequently antagonistic.

TABLE 5.—EFFECT OF NUTRITIONAL DEFICIENCIES ON PROTOZOAL INFECTIONS

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Human	Multiple	*E. histolytica*	Synergistic	Blumenthal *et al.*, 1947[40] Alexander and Meleney, 1935[7] Elsdon-Dew, 1949[93] Martin *et al.*, 1953[202]
Monkey	Multiple	*E. histolytica*	Synergistic	McCarrison, 1919[206b]
Guinea pig	Synthetic diet	Amebiasis	Synergistic	Lynch, 1957[194]
Human	General famine	Malaria	Antagonistic	Ramakrishnan, 1954[254b]
Rat	Starvation	*P. berghei*	Antagonistic	Ramakrishnan, 1953[254a]
Monkey	Multiple	*P. cynomologi* *P. knowlesi*	Antagonistic	Passmore and Sommerville, 1940[244]
Chicken	Vitamins A and B protein	Coccidiosis	Synergistic	Allen, 1932[8]
Guinea pig	Vitamin C	Amebic infections	Synergistic	Sadun *et al.*, 1951[257]
Monkey	Vitamin C	*P. knowlesi*	Antagonistic	McKee and Geiman, 1946[216] Geiman and McKee, 1948[115]
Mouse	Biotin	*P. berghei*	Synergistic (fatality) Antagonistic (parasitemia)	Ramakrishnan, 1954[254c]
Mouse	Pyridoxine PABA	*P. berghei*	Antagonistic	Ramakrishnan, 1954[254d]
Monkey	PABA	*P. knowlesi*	Antagonistic	Anfinsen *et al.*, 1946[11]
Duck	Niacin	*P. lophurae*	Synergistic	Roos *et al.*, 1946[273]
Chicken	Pantothenic acid	*P. gallinaceum* (blood induced)	Antagonistic	Brackett *et al.*, 1946[44]
Chicken	Pantothenic acid	*P. gallinaceum* (sporozoite induced)	No effect	Brackett *et al.*, 1954[44]
Chicken	Riboflavin	*P. lophurae*	Antagonistic	Seeler and Ott, 1944[300a]
Chicken	Thiamin Biotin Folic acid	*P. lophurae*	Synergistic	Seeler, Ott and Gundel, 1944[300c] Seeler and Ott, 1945, 1946[300b,d] Trager, 1943[339a]
In vitro duck cells	Folinic acid	*P. lophurae*	Synergistic	Trager, 1949, 1958[339b 339d]

TABLE 5 (cont'd)

Host	*Deficiency*	*Agent*	*Action*	*Reference*
Pigeon	B complex	*T. brucei*	Synergistic	Salazzo, 1929[290]
Rat	B complex	*T. equiperdem*	Antagonistic	Reiner and Paton, 1932[265]
Rat	Pantothenic acid	*T. lewisi*	Synergistic	Becker and Smith, 1941–42[24] Becker *et al.*, 1946–1947[25]
Rat	Biotin	*T. lewisi*	Synergistic	Caldwell and György, 1943, 1947[49a,b]
Rat	Thiamine	*Eimeria nieschulze*	Synergistic	Becker and Dilworth, 1941[23]
Rat	Pyridoxine Pantothenate	*Eimeria nieschulze*	Antagonistic	Becker and Smith, 1941–42[24]
Mosquito	Vitamin C	*P. gallinaceum*	Synergistic	Terzian, 1950[333] Terzian *et al.*, 1952, 1953[334 335]
Mosquito	Thiamine Niacin Pantothenic acid Biotin	*P. gallinaceum*	Antagonistic	Terzian *et al.*, 1953[334]
Suckling mouse	PABA (restriction in mothers)	*P. berghei*	Antagonistic	Hawking, 1953, 1954[136a,b]
Bird	Protein	*P. lophuræ*	Synergistic	Seeler and Ott, 1945[300c]
Mouse	Methionine	*P. berghei*	Antagonistic	Ramakrishnan, 1954[254e] Taylor, 1956[328]
Rat	Protein	*T. lewisi*	No effect	Caldwell and György, 1947[49b]
Mouse or rat	Milk diet plus vitamins	*P. berghei*	Antagonistic	Maegraith *et al.*, 1952[200] Hawking, 1954[136b] Ramakrishnan, *et al.*, 1953[256]
Monkey	Milk diet plus vitamins	*P. cynomologi* *P. knowlesi*	Antagonistic	Maegraith, 1953[199] Bray and Garnham, 1953[46]
Pup	Milk diet	*T. rhodesiense* *Babesia carus*	No effect	Maegraith, 1953[199]
Human	Milk diet plus vitamins	*P. vivax* *P. falciparum* *P. malariæ*	No effect	Chaudhuri and Dutta, 1955[57] Miller, 1954[229]
Chicken	Milk diet	*P. gallinaceum*	Synergistic	Ramakrishnan *et al.*, 1953[255]

The clinical observation that inadequate diets precipitate amebiasis has support from several sources. Prisoners of war are especially prone to develop amebic dysentery; with improved feeding dramatic improvement is usual[40,202]. In South Africa[93] fulminating amebic dysentery was common among maize-eating Bantus, rare among Indians on a rice and curry diet but with liver abscess relatively frequent; while Europeans on a balanced diet rarely

had either condition. Almost half of wild caught monkeys[206b] placed on milled rice diets developed amebic dysentery and died.

Malaria parasites *in vitro* have rather precise nutritional requirements[11,215,339c,339d]. Specific dependence on nutrients is indicated also by the pattern of antagonistic and synergistic response observed with various deficiencies. Judged by levels of parasitemia, the specific deficiencies antagonistic to bird, monkey and mouse malaria are vitamin A, vitamin C, riboflavin, pantothenic acid, and para-aminobenzoic acid[254e,300d]. Deficiencies synergistic with experimental infections of malaria include thiamine, niacin, biotin, folic acid and protein[114,279]; fatality is excessive and rapid in experimental malaria associated with either riboflavin or thiamine deficiencies[300a].

With one exception[265], trypanosome infections are reported as synergistic[49a,49b,290] with deficiencies of the vitamin B group. Biotin deficiency[25] had such an effect on rats infected with *T. lewisi* that hyperimmune serum gave no protection. Excess biotin administered after infection of biotin deficient rats had no therapeutic effect; indeed, the intensity of parasitemia sharply increased.

A further series of observations on protozoal infections are contrary to the general dictum that only deficiencies are of consequence in relation to infection. Both synergistic and antagonis-

TABLE 6.—EFFECT OF DIETARY EXCESS OF CERTAIN NUTRIENTS ON PROTOZOAL INFECTIONS

Host	*Diet*	*Agent*	*Action*	*Reference*
Dog	Liver (raw) or liver extract supplement	*E. histolytica*	Antagonistic	Kagy and Faust, 1930[156]
Dog	Ventriculin Solid residue of heated liver Canned salmon	*E. histolytica*	Synergistic	Faust and Kagy, 1934[96] Faust *et al.*, 1934[97]
Dog	Intracecal injection of salmon	*E. histolytica*	Antagonistic	Faust *et al.*, 1934[97]
Dog	Intracecal injection of tryptic and peptic digests of salmon	*E. histolytica*	Synergistic	Faust *et al.*, 1934[97]
Guinea pig	High protein (50% casein)	Amebiasis	Synergistic	Taylor *et al.*, 1952[330]
Rat	Animal protein excess	Trichomonas	Antagonistic	Hegner and Eskridge, 1935[139a]
Rat	High carbohydrate diet	Trichomonas	Synergistic	Hegner and Eskridge, 1937[139b]
Human	Vitamin C excess	Malaria	Antagonistic	Mohr, 1943[232]
Chicken	Thiamine excess	*P. gallinaceum*	Synergistic	Seeler and Ott, 1946[300d] Rama Rao and Sirsi, 1956[253]
Mouse	Meat protein excess	*P. berghei*	Synergistic	Ramakrishnan, 1954[254c]
Mouse	Protein (10%, 20%, 30% casein)	*T. congoleuse*	Antagonistic	Keppie, 1953[161]

tic effects have been observed with an excess of nutrients, Table 6. Administration of an excess of either thiamine or riboflavin to animals with experimental malaria and deficient in these vitamins resulted in a sharp increase in parasitemia[300a,300d]. An extremely active research has developed from the observation that a milk diet suppresses rat[136b,200] and monkey malaria[199].

Mechanisms in Synergism. Distinctive patterns of interaction in respect to main classes of microbiologic agents of disease and kinds of malnutrition have been identified and listed in the preceding section. Possible mechanisms accounting for those groupings are now considered.

Genetic Constitution of Host. Synergistic and antagonistic interactions are best seen in populations of heterogeneous genetic origin[295d,296,356]. The less homogeneous a population the broader is the range within which nutritional factors influence infection. The possibilities may be listed as follows: (1) Natural or constitutional resistance is so high relative to agent potential that disease will not result from infection, no matter how nutrition is varied. (2) Natural or constitutional resistance is so low in relation to potential virulence of the agent that severe infectious disease will ensue regardless of nutritional factors. (3) Natural or constitutional resistance is in such balance with agent potential that nutritional factors may influence the course of infectious disease to a greater or less extent. Successful attempts to measure the effect of nutritional factors are limited to the last situation; since people and microorganisms vary, it is more common among natural populations than the other two.

Specific Host Factors. An association of deficiency and infection often produces an opposite response with different hosts. Ratcliffe[263a,263b,264] developed a method of standardizing tuberculous infections through inhalation of as few as five tubercle bacilli. Guinea pigs and hamsters on 5 to 6% casein showed more rapid progression of infection than those receiving 25% casein, while the disease in rats progressed most rapidly in animals given 25 to 40% casein.

Age of the host also influences the pattern of interaction. The usual increased resistance to avian encephalomyelitis infection[72] of thiamine deficient 2-week old chicks was reversed by using day-old chicks. Sabin and coworkers[284,285,286] reported an opposite influence in 2- to 4-week old mice exposed to the virus of vesicular stomatitis. Mice of this age normally develop "maturation resistance" to infection presumably localized at the peripheral nerve endings since animals continue susceptible to intraneural or intracerebral inoculation. By placing either mothers or weanling mice on diets deficient in B-complex, thiamine, vitamin E or restricted total calories, marked retardation was noted in appearance of this normal resistance. A similar mechanism may account for the established observation that only infant mice are susceptible to Coxsackie virus.

Vitamin Deficiencies and Antibody Response. Because of ease and exactness in measurement, antibodies have had major attention in efforts to evaluate end results of coincident infection and malnutrition. Most specific vitamin deficiencies interfere with antibody production in the experimental animal. Although antedated by a number of investigations[67a,271], that of Blackberg[36] in 1928 is one of the first having controls. Killed typhoid bacilli or small doses of live bacilli injected into rats deficient in vitamins A and D resulted in measurably lower titers of agglutinin and bacteriolysin than in control ani-

mals. Similarly[241], bacteriolytic and agglutinating response of sheep to *E. coli* and S. *choleraesuis* was lower in animals fed on poor pasture or denied access to grass.

Pyridoxine deficiency[321,322] decreased the response of rats to sheep erythrocytes. Hemagglutinin response in rats inoculated with human erythrocytes was impaired by dietary deficiencies of biotin, thiamine[14a], riboflavin and especially of pantothenic acid and pyridoxine[15]. Paired feeding trials proved the result was due to specific vitamin deficiencies and not to decreased food intake[191]. Further studies[190] showed that deficiencies of vitamin A, niacin and tryptophan also had a depressing effect on antibody response, pteroylglutamic acid deficiency still more so, and vitamin D deficiency not at all.

Wertman *et al.*[361,362a,362b,362c] investigated vitamin deficiency states in development of complement-fixing antibodies in the rat against rickettsiae of murine typhus. Single deficiencies of pantothenic acid, thiamine, pyridoxine, riboflavin, folic acid and vitamin B_{12} each resulted in reduced antibody response to small doses of rickettsiae; with large immunizing doses the effect was evident only with pyridoxine. Niacin deficiency and food restriction in pair-fed controls had no effect. Rabbits on a diet deficient in pantothenic acid were injected with typhoid-paratyphoid vaccine with and without pantothenic acid[225] and tested 10 and 45 days later by Widal reaction. Gamma globulin values[225] and agglutinin titers[224] were higher in vitamin fed groups; the number of animals used was not mentioned.

In a recent summary of his studies, Axelrod[14c] makes clear that adequate nutrition is required for both primary and secondary response to an antigen. By administering deoxypyridoxine shortly before secondary immunization of rats with diphtheria toxoid, the induced pyridoxine deficiency interfered with the secondary response of antibodies even after a normal primary response.

Most if not all of the effect of vitamin deficiency on antibody formation presumably is due to interference with protein synthesis[14a,14b] and indeed specific roles in protein synthesis are known for many of the vitamins. Similar effects have been obtained by experimental use of amino-acid analogues[318b].

Protein or Amino-acid Deficiencies and Antibody Response. Madden and Whipple[198] reported that dogs depleted of protein by repeated plasmapheresis had reduced ability to elaborate specific antibodies; the animals were more susceptible to infection[228], a change that could be reversed by protein feeding. By similar methods Cannon *et al.*[51] observed a lesser capacity of rabbits to produce agglutinins to S. *typhosa* and S. *paratyphi*, and explained it on the basis of insufficient protein for synthesis of gamma globulin. Subsequent work[31,32,116,367] led to firm conclusions that protein deficiency not only interferes with antibody production but also affects phagocytosis, qualitatively and quantitatively.

Attempts by a number of investigators to demonstrate a similar effect in man have ended in failure[33,135,177], probably because the protein deficiencies were not sufficient to induce a significant fall in serum protein fractions. Inability to demonstrate diminished antibody response in patients with chronic wasting diseases[20], mainly carcinomas, could have been due to inanition rather than protein deficiency as claimed. A greatly slowed antibody response to typhoid vaccine was observed by Wohl *et al.*[368] in 88 patients with serum albumin values below 4

gm. per 100 ml., compared with 14 similar patients given special supplements of protein or protein hydrolysate. No observations have yet been made on antibody response in kwashiorkor, a severe and widely prevalent protein malnutrition of children.

Antibodies formerly were assumed to originate from preformed serum protein components. Recent use of radioactively labeled amino-acids[122,125,326] indicates that antibodies may be synthesized directly from amino-acids. The initial lag between injection of antigen and immunologic response may well be the interval required for synthesis of antibody-forming enzymes, rather than for elaboration of template protein as initially suggested by Cannon[50a,50c,50d].

Antibody response is not the sole factor in resistance to infection[16,98c]; in a number of infectious diseases, reduction in ability to form antibodies is not associated with greater severity. For example, Zucker *et al.*[378] found no relationship between the decreased ability of rats to form agglutinins to a vaccine prepared from killed cultures of *C. kuscheri*, and resistance to infection with this organism. Similarly, Miles[227] saw no significant difference in agglutinin response of rats in protein deficiency states, despite the more severe disease in deficient animals. As Schneider[295g] has pointed out, if the effect of nutritional deficiencies is merely to slow rather than block formation of antibodies, the ultimate effect on resistance may not be great.

For observations in experimental animals to have practical application to clinical medicine, deficiencies must match those present in ordinary human diets. Opportunity for proof at a high level of deficiency is to be found in many parts of the world in kwashiorkor, xerophthalmia and infantile beriberi. The malnutrition of children studied by Kahn *et al.*[157], while stated to be severe, was not sufficient to warrant the generalization that "in man, unlike laboratory animals, malnutrition does not impair immune-body production."

Evidence supports a view that a number of severe nutritional deficiencies can interfere adversely with antibody response; in some diseases and in some hosts this may result in demonstrable synergism with the infectious agent. The deficiency necessary for such an effect is not commonly encountered in man in technically developed countries but is common in regions where food supply is inadequate. However, the adverse effect on antibody response is only one of several mechanisms active in observed synergistic effects of malnutrition and infection.

Reduced Phagocytic Activity. Some evidence[189,233] exists that a number of nutritional deficiencies[6,14c,318a] depress reticuloendothelial activity thus affecting both antibody production and phagocytic activity.

No characteristic alteration in number or distribution of leukocytes[140,342] occurs in vitamin A deficiency, but phagocytic activity is depressed in both rats[74] and humans[134]. Rats, rabbits and pigeons[359,360] fed on diets deficient in vitamin A and B-complex had a normal opsonic index but the rate of phagocytosis of bacteria injected into the peritoneal cavity was definitely lowered[242]; the inoculated paratyphoid bacilli were removed and destroyed in liver, spleen and peripheral lymph nodes. Animals receiving a heavy infecting dose or having vitamin A deficiency[178a,178b] developed secondary bacteremia with subsequent severe and often fatal disease.

Scurvy in guinea pigs has been associated with decreased numbers of granulocytes and lesser phagocytic power[181, 237]. In scorbutic animals, intraperitoneal

injections of irritating substances failed to produce the exudate clouded by pus cells characteristic of normal animals.

From experimental and clinical studies Doan[83] concluded that folic acid deficiency produces cellular inadequacy in mammalian bone marrow, interfering with production of phagocytes to such extent as to nullify the effect of protective antibodies. Others have had difficulty[185] in maintaining folic acid deficiency in macacus monkeys because of frequent leukopenia, severe dysentery and death. When fed a deficient diet[292] these animals develop a striking granulopenia, accompanied by markedly lowered resistance to spontaneous infection, and to experimental infection with Group C hemolytic streptococci or influenza virus, in all instances with high fatality.

Because severe protein depletion leads eventually to marked atrophy of liver, spleen and bone marrow[26,52,340] where most phagocytic cells are presumed to originate, normal production of phagocytes should be inhibited. Supporting evidence comes from the work of Guggenheim and Buechler[127b,127c] that protein deficient diets "invariably" impair leukocyte regeneration in rats; dietary protein reversed this effect, the result depending on what was fed as well as amount. Leukocyte replacement was related to growth promoting characters of the diet, except that peanut protein promoted blood regeneration more than growth[127e]. Optimal amino-acid patterns for growth and for maintenance of resistance may not be identical[9].

Most infections superimposed on kwashiorkor give rise to no more than a feeble leukocytosis; children with this disease are notoriously susceptible to intermittent infection[340].

Severe undernutrition produces no uniform effect on phagocytes[155]. Balch and Spencer[21] found normal numbers of circulating neutrophils in the last stages of prolonged wasting disease, while Livieratos *et al.*[189] report functional impairment of the reticuloendothelial system.

Altered Tissue Integrity. Dietary deficiencies have long been assumed to decrease resistance to infection through adverse effects on the integrity of epithelial tissues. If sufficiently severe, gross lesions of epithelial surfaces appear, such as angular stomatitis, cheilitis, dermatitis and enteritis in deficiencies of vitamins of the B-complex, the gum changes in scurvy, and the pellagroid skin lesions and atrophy of intestinal mucosa in kwashiorkor.

Pathological changes incident to nutritional deficiency conceivably influence resistance through a variety of mechanisms[148], with no present means to judge relative significance. The main possibilities are (a) increased permeability of intestinal and other mucosal surfaces, (b) reduction or absence of mucous secretions, (c) accumulating cellular debris and mucus[237] to give a more favorable culture medium, (d) alterations in intercellular substance by deficiencies such as scurvy[221], (e) interference with normal tissue replacement and repair, (f) loss of ciliated epithelium in the respiratory tract or (g) nutritional edema with increased fluid in the tissues[332].

Mellanby and Green[218] demonstrated metaplasia and keratinization of respiratory epithelium in rats as a result of vitamin A deficiency, a condition conceivably favoring penetration of the mucosal barrier by infectious agents. Wolbach and Howe[369] arrived at a similar conclusion, and Mellanby[219] reported comparable changes in dogs deficient in vitamins A and D. Recently Weaver[355b] demonstrated that the mucosa of parts of the gastrointestinal tract of cotton rats is more readily penetrated by poliomyelitis virus when the

diet is deficient in vitamin A. Salmonella penetration to the viscera of rats was shown to be enhanced in deficiencies of vitamin A, riboflavin, biotin and protein[127d,166]. By contrast absorption of botulinus toxin was not increased by vitamin A deficiency[323].

Frye[110] believes that resistance to most intestinal parasites is a property of the local intestinal mucosa. Lynch[194] produced fulminating amebiasis in guinea pigs by a special synthetic diet which altered bacterial flora. Since this result could not be reproduced by feeding massive doses of bacteria derived from the lesions, attention was directed to local causes; a thinning and vacuolation of the mucosa was thought accountable. Grant[121] also produced alterations in the permeability of the intestinal wall of guinea pigs to a human strain of tubercle bacillus by manipulating calcium, vitamin C and vitamin D in the ration.

Interference with Nonspecific Protective Substances. In many instances, an observed variation in "bacteriocidal power" is impossible to relate to a specific mechanism, either antibodies or nonspecific substances. Blood serum of rachitic rats had considerably lower bacteriocidal effect on *S. typhosa*[243,310] and staphylococci[99] than serum from normal rats. Swartz, Alicata and Lucker[325] described specific growth-inhibiting substances in horses and rats that retarded development of intestinal nematodes; nutritional deficiencies interfered with this process. In the extensive studies by Guggenheim and Buechler[127b] the peritoneal fluid of rats deficient in thiamine, riboflavin or vitamin A had decreased capacity to destroy inoculated *S. typhimurium*.

Anderson[10] reported greatly reduced lysozyme in tears of 2 children with xeropthalmia which "increased remarkably with 5 to 7 days of cod liver oil therapy." Increased lysozyme has been reported[324] in human vitamin A deficiency. Dawson and Blagg[79] tested saliva from patients with cholera, others with severe malnutrition, and from healthy controls against a variety of infectious agents. Saliva from cholera patients and the malnourished group had little or no antibacterial action compared with controls.

The significance of these sparse observations is difficult to assess. No agreement exists on the importance of lysozymes. Less is known of other nonspecific antimicrobial substances. The possible effect of nutrition on properdin levels[144,351] warrants investigation.

Nonspecific Destruction of Bacterial Toxins. Resistance to bacterial toxins ordinarily is considered a function of antibodies. Additional ways are possible. In the experience of Werkman *et al.*[360] rats suffering from deficiencies of B-complex vitamins or vitamin A were more susceptible than controls to diphtheria toxin, although antitoxin production was equal and rate of disappearance of injected toxin was normal.

Skin reactivity of scorbutic guinea pigs to diphtheria toxin was increased[12] and survival time following parenteral injection reduced[34,162]. Rats[36] deficient in vitamins A and D and also vitamin B-complex were 40 to 100 times more susceptible to tetanus toxin than controls. Sheep on diets low in minerals and in vitamins A and D reacted more strongly than controls to intradermal injection of toxin of the bacillus of lamb dysentery[197]. Torrance[338], however, could not confirm previous results, including his own, that vitamin A content of the liver was in any way correlated with survival of guinea pigs following injection of either diphtheria or tetanus toxin.

Brief fasting[87a] as well as feeding deficient diets had an influence on the susceptibility of mice to endotoxin of

Klebsiella pneumoniae; lesser doses were required for a fatal result, which occurred a few hours after injection and long before an immune response would be expected. Conditions were reversed after 48 hours on a good diet.

Alterations in Intestinal Flora. Intestinal synthesis of some essential nutrients depends upon the bacterial flora of the intestine[64]. The action of diet on symbiotic bacteria can have an independent influence on growth and development of experimental animals. By intubating patients with sprue, Frazer[109] proved that the bacterial flora of the colon moves high into the small intestine in large numbers and presumably competes with the host for B-complex vitamins before they can be absorbed.

Changes in bacterial flora caused by diet sometimes have a favorable and sometimes an unfavorable influence on symbiotic and pathogenic parasites. In guinea pigs[194] a synthetic diet drastically altered the bacterial flora and intestinal mucosa; presumably this contributed to the fulminating amebic dysentery that followed. Hegner[138] was impressed by the rarity of intestinal protozoa in many carnivores; he found that rats fed high animal protein diets were less favorable hosts for *Giardia muris, Trichomonas muris* and *Hexamitus muris* than animals subsisting mainly on vegetable proteins and carbohydrate. Diets of herbivores are stated to lead at times to alimentary stasis, thereby favoring production of toxin by *Clostridium welchii*[270].

Altered Endocrine Balance of Host. Altered endocrine function is probably involved in some of the mechanisms previously presented. Endocrine involvement in nutritional synergism and antagonism with infections is almost wholly unexplored. On the effect of protein and choline deficiency in lowered adrenal function, as well as the less direct relationship of ascorbic acid deficiency, Kinsell[163] states that "it has been well established that the resistance of the Addisonian patient or the adrenalectomized animal to infection in particular and to stress in general, is markedly diminished." Despite evidence that cortical hormones may have a direct inhibiting effect on certain bacterial endotoxins[42,113], the general mechanism of corticoid action in infection is not clear. Selye[302] states that low carbohydrate diets "augment the efficacy of both corticotropin and of corticoid steroids;" this may be responsible for the depressed resistance commonly observed.

Infection is a common and severe complication in diabetes, although notably less with long-acting insulin preparations. Huge nitrogen loss once was common during the short period of ketosis associated with regular insulin. Pollack[249] believes that maintenance of positive nitrogen balance with protamine-zinc insulin, even with glucosuria, is the key to the better resistance to infection characteristic of diabetics under modern management.

Nutrient in Excess of Host Requirements. Therapeutic use of nutrients to control infection has led to much uncritical enthusiasm. Only a few studies meet even elementary scientific criteria and merit mention. An *in vitro* antibacterial action of vitamin C has been repeatedly demonstrated[234,236]. Hill and Garren[142] in well controlled experiments on 40 groups of 40 chicks infected with salmonella showed that resistance was increased by large doses of all the known vitamins if an antioxidant was present. The fact that either ascorbic acid, which is not known to be a dietary requirement of chickens, or diphenylene diamine could be used to provide the anti-oxidant effect suggested a nonspecific action.

Excess biotin given to deficient rats

infected with *T. lewisi* produced a sharp increase in numbers of parasites[25]. Wooley and Sebrell[371] having demonstrated the synergism of deficiencies of riboflavin and thiamine in either *ad-libitum* or paired-fed mice with Type I pneumococci then showed that doses of either of these vitamins ten times greater than in the control diet increased mortality. It is possible that the high doses caused an imbalance of some other nutrient to produce a relative deficiency. In detailed investigations on the interaction of specific deficiencies with avian malaria, a phenomenon of interest was the abrupt rise in parasitemia observed when therapeutic doses of either riboflavin or thiamine were given to deficient birds[300d].

Suppression of malaria by diets of milk supplemented only with vitamins was reported by Maegraith *et al.*[200] in *P. berghei* infections of mice. This finding has been confirmed in malaria of monkeys but reports in humans are conflicting[46,57,229]. Infections relapsed when the mice were placed on a normal diet; subinoculation during suppression showed that a few parasites were present. Hawking[136a] attributed the suppressive action to the relative absence of para-aminobenzoic acid in milk at certain seasons and claimed that its addition abolished the suppressive action. The suggestion is that this nutrient is essential to the malarial parasite but not to the host. Ramakrishnan[254d] found that methionine and pyridoxine also caused the parasitemia to return to high levels. Ramakrishnan *et al.*[257] have now reported the isolation of a milk-resistant strain of *P. berghei.*

Mechanisms of Antagonism. Evidence already introduced establishes the generalization that antagonism is a common manifestation of nutritional deficiency when associated with viral and protozoan infections; it is relatively uncommon in rickettsial, bacterial and helminth infections. These effects seemingly result from dependence of certain infectious agents on the biosynthetic processes of host cells, which in turn require specific metabolites. The many studies on nutrient requirements of viruses are beyond the scope of this review[94,147].

Viruses are among the more resistant infectious agents to chemotherapeutic attack[107]. They are known to divert certain enzyme systems of host cells to the synthesis of viral precursors. Recent studies by tissue culture show with increasing precision specific enzyme and metabolite requirements, with RNA (ribonucleic acid) occupying a key role[56]. For growth of the virus of psittacosis in tissue culture[18] only the following amino-acids are essential: tyrosine, threonine, methionine, isoleucine, phenylalanine, tryptophan, leucine, valine and cystine; of these cystine and tyrosine are not required in human nutrition if adequate methionine and phenylalanine are present. Such observations have obvious potential in indicating future methods of treatment[64,98c, 285,286]. The more complex host frequently can compensate for altered metabolic systems by alternative enzymes or nutrients.

Research directed toward retarding enzyme systems essential to the parasite but not necessary for the life of the host is closely linked with the growing attention paid to metabolic antagonists. The detailed studies on metabolites, antimetabolites and enzyme inhibitors in relation to growth of vaccinia virus[336] are in good illustration. Metabolic antagonists of vitamins have been used to demonstrate both synergistic and antagonistic effects. Bodian[41] showed that pyridoxine deficiency in monkeys induced by deoxypyridoxine decreased resistance to poliomyelitis. Although paralysis almost never follows

oral infection of normal monkeys with poliomyelitis, 3 out of 12 pyridoxine deficient monkeys developed severe paralysis when given virus by mouth. Using chick embryos Cushing *et al.*[76] have demonstrated that the thiamine analogue, oxythiamine, caused complete suppression of mumps virus and partial suppression of influenza virus; deoxypyridoxine caused complete inhibition of both viruses.

Wooley and Murphy[370] have reported *in vitro* studies in which pyridoxine deficiency induced by deoxypyridine inhibited the development of *E. coli* bacteriophage but had no effect on growth of the bacteria. Since this effect was reversed by pyridoxine and by such compounds as acetic acid, propionic acid, glycine and butyric acid, the authors suggest that pyridoxine deficiency blocks the utilization of glucose by the bacteriophage.

Rickettsiae multiply[376] best in host cells which have little metabolic activity in contrast with viruses which grow best in rapidly metabolizing cells. It seems probable that the rickettsiostatic effect of para-aminobenzoic (PABA) acid[124,246b] is due to the ability of this compound to increase metabolism of host cells. Folic acid, although it has PABA as part of its molecule does not have an equivalent effect in inhibiting the rickettsia of typhus fever.

Much work on the biochemistry and physiology of protozoa[44,193] indicates that many of the assumptions stated above in reference to viruses apply also to highly parasitic protozoa. The important criterion again appears to be the degree of dependence of the organism on the metabolic systems and nutrition of the host.

Nutritional requirements often vary according to the developmental stage of the parasite. For example, pantothenic acid is adequate for survival of intracellular forms of *Plasmodium falciparum*[339c] but culture of extracellular forms requires formed coenzyme A; folic acid permits growth of intracellular forms but folinic acid is required in extracellular cultures. Both para-aminobenzoic acid and folic acid enhance parasitemia in infected ducks[339d]; infected erythrocytes actually contain more folic acid.

Antagonism between malnutrition and infection is rare among bacteria and helminths; examples of interference with the metabolism of the agent are correspondingly scarce. The similarity of enzyme systems in *Schistosoma mansoni* and in the mammalian host implies[47a,47b,47c] that factors interfering with the metabolism of host cells also may be expected to interfere with worm development, but other effects of malnutrition on resistance may overweigh this.

A striking example of natural antagonism is the discovery that virulent strains of S. *typhosa* require cystine and tryptophan while avirulent mutants also need a purine[102]. Mouse peritoneal fluid normally is lacking in purine. An avirulent strain became virulent when a purine, xanthine, was injected intraperitoneally or when the organism reverted to purine independence.

Although failure to meet the nutritional needs of the infectious agent provides a ready explanation for antagonism, the practical importance of this mechanism has been overestimated. Melnick[220] pointed out that nutritional deficiencies usually result in antagonism only when the animal is in such deficient state as to be almost moribund; he believes that in most mild deficiencies virus and host cell compete for a nutrient, with the virus seemingly having priority. Under these circumstances, any advantage to the host in combating the virus is offset by the adverse effects of malnutrition, including synergism with secondary

infections and interference with convalescence.

The mechanisms involved seem to preclude the use of dietary deficiencies as control measures in most situations where antagonism is known to occur. Some specific metabolic antagonists, however, block reactions of vital importance to the agent and of lesser importance to the host. Information as to the enzymatic and metabolic influences of diet on specific enzyme systems in animals of the kind recently summarized by Knox *et al.*[167], needs to be correlated with knowledge of the specific biochemistry and physiology of microorganisms.

Influence of Infection on Nutritional Status. Discussion thus far has been confined to the influence of nutrition on the course of infection. Conversely, most infections have a deleterious effect on nutritional status, a fact insufficiently recognized. At a recent three-day conference on Nutrition in Infections[230] no principal speaker mentioned this feature of the problem.

Infection and Protein Metabolism. Kwashiorkor is a major factor in the high mortality among preschool children characteristic of at least 50 technically underdeveloped countries[28,297]. The symptoms are commonly precipitated by an acute infection[13,81,153,299]. Either diarrhea[26,340] or measles[252] is most often responsible, but any infection may be involved. Seasonal increase in hospital admissions and deaths attributable to diarrhea often precedes a similar rise in kwashiorkor by 4 to 8 weeks[27,119]. Kwashiorkor can originate in dietary deficiency alone, but most cases are the result of synergism between infection and protein malnutrition.

In many cultures solid foods, especially those of animal origin, are traditionally withdrawn from children with intestinal and other infections; thin cereal or starch gruels become the diet. Furthermore, a child with infectious diarrhea is likely to be given strong purgatives for worms, mistakenly blamed for the diarrhea[153,299]. These practices hasten the appearance of frank protein deficiency.

Infections have long been known to exert a strongly unfavorable effect on nitrogen balance. In 1910 MacCallum[196] cited a German case in which the nitrogen equivalent of 2.5 kg. of muscle was lost in 8 days of fever. Increased urinary nitrogen excretion has been demonstrated in malaria[22], pneumonia and streptococcal infections[91], erysipelas[69], pyelonephritis and paratyphoid[168], typhoid[70,171], tuberculosis[205,258], and meningitis[126]. Loss of urinary nitrogen is partly from greater energy requirements imposed by higher body temperature, but mainly from toxic destruction of protein[245]. Nitrogen loss may continue long after fever has subsided[126,276] or may begin during the prodromal period before fever and clinical signs appear[30]. Similar nitrogen loss occurs in dogs with sterile abscesses and minimal febrile reaction[71,77,373].

Chronic infections also have an adverse influence on protein metabolism; hypoproteinemia may develop despite normal protein intakes[50b] and dietary protein supplements are less effective[348].

Nitrogen loss in infections has particular significance in young children because of high requirements for protein per kilogram of body weight. Negative nitrogen balance in infectious diarrhea may occur despite intake of 2 or more grams of protein per kilogram per day[61,260,276]. Close[68] described a child with kwashiorkor whose serum albumin increased in 7 weeks from 1.05 to 3.58 gm. per 100 ml.; the patient then contracted typhoid fever and the level fell promptly to 1.59 gm.

Decreased absorption of nutrients

from the gastrointestinal tract probably plays a minor role even in infectious disorders. In scarlet fever[343b] control of pancreatic enzyme was reduced, presumably a common occurrence in other infections. Nevertheless where fecal nitrogen has been measured, the increase is small.

Intestinal helminths can interfere with protein digestion by competing with the host for nitrogen, producing antiproteolytic enzymes and damaging the intestinal mucosa[47a,146,291]. For example, significant increases in nitrogen have been demonstrated in Indian children after treatment for ascariasis[344]. Both *Ascaris lumbricoides* and *Strongyloides edentatus* have enzymes not only for utilization of carbohydrate[278a], but for the digestion of protein[278c] and fat[278b]. *Trichinella spiralis* in rats[278d], *Trichostrongylus colubriformis* and mixed nematode infections in lambs inhibited protein digestion[108]. Eleven nematode species have been shown to decrease protein absorption in sheep[320].

Infections with intestinal protozoa occasionally reduce nutrient absorption. Véghelyi[343a] has shown that increased fat in stools of children with *G. lamblia* is due to impaired absorption. He related this to his observation in rabbits of as many as 1,000,000 giardia per square centimeter of mucosa. Under such circumstances absorption of nitrogen could be affected.

Infection and Vitamin Deficiencies. Infection may precipitate frank clinical signs in individuals with subclinical vitamin deficiencies. It has long been known that infections can cause florid scurvy in persons on a diet low in vitamin C[141a]. Either experimental trypanasomiasis[235] or tuberculosis[34] may hasten the appearance of scurvy in guinea pigs.

Diarrheal and other infections may decrease serum vitamin A levels[152,305] and more importantly precipitate xerophthalmia, keratomalacia and even blindness[38,239,314]. Giardiasis sometimes interferes with vitamin A absorption in children[59,158]. In Japanese prison camps beriberi developed in more than half of persons with dysentery[308]. There can be no doubt that infections contribute to the production of frank vitamin deficiencies in poorly nourished populations.

Infection, Growth and Development. Children recovering from kwashiorkor fail to gain weight when intercurrent infection is present and may lose weight despite high intake of calories and protein; once the infection ends the weight curve resumes an upward trend[298]. Children on a low protein diet had pronounced and protracted depression of growth after respiratory infections[358]; well-nourished children had only transient weight loss. Conversely, an effective control program for malaria and filariasis resulted in a spurt in growth by West African village children[213]. Rates of growth and maturation are relatively sensitive indicators of adverse metabolic influence from infection.

Infection and Anemia. Infections significantly reduce hemoglobin levels even with an adequate diet[63,132]. In Uganda, Trowell *et al.*[340] found that severe bacterial infections including pneumonia, meningitis, septicemia and tuberculosis caused anemia, sometimes suddenly. Mildly anemic[48] patients with tuberculosis, chronic lymphangitis, or pneumonia had marked inhibition of bone marrow with shortened erythrocyte life span, as demonstrated by radioactive isotypes of iron.

Chiriboga *et al.*[60] reported macrocytic anemia to be common among poorly nourished patients with malaria, and microcytic anemia in those with hookworm. With associated malaria and hookworm, the two types of anemia were equally frequent. Low

serum iron levels are stated to be the most constant feature of anemias associated with infections in man[53a].

Extensive information is available on anemias of experimental infections. In pigs either staphylococcal infection or sterile turpentine abscesses[53b,365] resulted in a pronounced hypoferremia and anemia. In fasting dogs either endometritis or sterile abscess interfered with hemoglobin production[277]. Spontaneous infection in monkeys or sterile turpentine abscesses resulted in folic acid deficiency and megaloblastic anemia[204], suggesting that additional vitamin B_{12} or folic acid was required during severe or prolonged infection.

That hookworm infection reduces weight, strength, stamina and performance of adults and contributes to retardation of both physical and mental growth of children is well established[174]. The study of Rhoads *et al.*[266a, 266b] in Puerto Rico, supported by many others, shows that addition of iron even without antihelminthic treatment gives marked improvement in anemia. By competing with the human host for vitamin B_{12}, the cestode, *Diphyllobothrium latum*, has been shown to cause a form of macrocytic anemia[346a,346b,347].

Areas for Research. Certain lines of investigation appear especially promising in furthering knowledge of interaction between nutrition and infection.

Field Studies on Human Populations. Community programs for improved nutrition should include measurement of the impact of diet on extent, course and frequency of infectious disease[120], as well as the more conventional appraisal of physical development and nutritional status. This applies especially to the many studies now in progress on kwashiorkor. The strong association between infection and the subsequent appearance of frank malnutrition in infants and young children needs systematic exploration, particularly during the difficult period of transition from breast feeding to an adult diet.

Dependable information on morbidity and mortality is regularly lacking in countries where infant mortality is great. Field studies provide the only practical means of acquiring this essential information for some time to come. The feasible procedure is to incorporate such effort in activities of the health demonstration centers now developing in many countries.

Even in technically developed countries, individual cases of malnutrition will be encountered in clinical practice, by reason of environmental or genetic factors. The influence on staphylococcal and common respiratory infections merits study.

Experimental Studies on Laboratory Animals. The value of laboratory investigation is in testing hypotheses and exploring individual clues derived from clinical and epidemiological observations. Specific deficiencies from single nutrients can be produced and their effect evaluated; in the field most deficiencies are multiple and mixed. Interaction of induced deficiencies with infection by strains of an infectious agent of known virulence can be identified in host animals of pedigreed genetic background. Such specificity is important in defining mechanisms and determining possible control measures. The results should not be extrapolated to human populations without proper field investigation.

Many laboratory studies of the past suffer from poor experimental design and analysis; the present is not exempt. Some 10 years ago an outstanding conference[65] of workers in the field codified ground rules for the conduct of such investigations. For the particular purpose of determining interaction between infection and nutrition, they may

be enlarged and modified as follows: (1) The fundamental importance of the genetic constitution of both host and parasite has been repeatedly demonstrated. (2) Infections of a type occurring spontaneously in the animal host, or with a clinical reaction in laboratory animals paralleling that in humans, are generally preferred as subjects for study. (3) If a natural portal of entry is possible, the practical value of the results commonly is greater than for infectious agents introduced artificially, especially where local trauma is involved. (4) Dose and virulence of the infectious agent requires careful control. Since nutrition studies commonly extend over long periods, the agent should be suitably stored to provide a stable preparation for continuing experiments. (5) There is need for precise definition of nutritional deficiencies, distinguishing particularly those due to specific nutrients and those incident to inanition or dehydration, through lesser palatability, decreased appetite, or inability to assimilate food and water. Severe and highly specific deficiencies can be produced by antimetabolites, a technique of proven usefulness in pyridoxine, thiamine and other deficiencies. Greater use can be made of paired feeding, but not to exclusion of ordinary controls which provide conditions more nearly comparable with natural situations. (6) The level of the deficiency should be controlled and recorded. Interaction is possible within limited ranges and at low levels of deficiency. The competition for nutrient between host and agent needs to be evaluated. (7) Virus studies show that duration of deficiency is sometimes important; reversals between antagonism and synergism have occurred as deficiencies pass from acute to chronic stages. (8) Criteria for measuring resistance should be specified; more than one measure of resistance is desirable, such as survival, production of antibodies, phagocytic activity or localization of pathogenic organisms. (9) Attention to factors such as age, weight, sex, segregation of litter mates, physical condition of cages, likelihood of coprophagy, variation in intestinal flora, temperature and humidity of the laboratory are basic elements in good experimental design. (10) The numbers of experimental animals should be sufficiently large to permit satisfactory statistical appraisal of results, with consideration of the advantages of factorial methods of design and analysis. (11) Appropriate controls include uninfected animals on the deficient diet, normal animals receiving the infectious agent, and normal animals given the medium or normal tissue without the agent, the latter because of possible nutrients in this material.

Biochemistry and Metabolism of Infectious Agents. Investigation of specific nutritional requirements of such readily cultured infectious agents as the bacteria is now extended by modern techniques to those requiring living cells for multiplication or having a direct parasitic relationship to host metabolism. The possibility of new means for biochemical control of infectious agents by interfering with their metabolism has progressed beyond the speculative stage; the usefulness of the sulfonamides rests in their ability to act as metabolic antagonists to para-aminobenzoic acid. Ways of reaching intracellular agents by acting on their metabolic processes through the enzyme systems of host cells are under study. The dependence of viruses on the enzyme systems of host cells has been well demonstrated[107]. A possible attack is that host cells may have alternate metabolic systems permitting substitution of nutrients, while viruses and other agents presumably are more limited in the biosynthetic processes

used. If specific nutrients are found essential to a microorganism but not required by host cells, experimental efforts to produce these deficiencies by metabolic analogues become logical.

Mechanisms of Synergism and Antagonism. Although agent metabolism probably will continue as the primary interest in studies of antagonism, other mechanisms of interaction are possible. Research in synergism should escape its present major restriction to measurement of antibodies. Properdin[144] and other nonspecific factors in resistance, such as rate of cellular metabolism, edema versus dehydration of tissues, the balance of electrolytes and endocrines, and types of inflammatory response all merit consideration. More information is needed on optimum diets for convalescence.

Some Common Misconceptions. A frequent inclination to dismiss the association of nutrition and infection as of little practical importance is based on the following erroneous interpretations of existing data. (1) Examples of antagonism are such spectacular departures from previous concepts that they are sometimes overemphasized and considered the prevailing type of relation. Comment: The preceding tables and text demonstrate the greater frequency of synergism over antagonism. (2) Much published information claiming synergism fails to meet modern standards of scientific evidence, with the result that the basic concept is put in doubt. Comment: Many well designed and executed studies leave no doubt of the frequent occurrence of synergism. (3) Since antagonism does occur, a poor diet might be advantageous to an infected host. Comment: Poor diet is neither an accepted nor an effective therapeutic measure; even where antagonism exists, such a diet under natural conditions will delay convalescence and lead to synergistic appearance of secondary infections, increasing the threat to survival. (4) The degree of malnutrition necessary to produce synergism and antagonism in experimental animals does not occur in populations of man or domestic animals. Comment: This comes from incomplete knowledge of the seriousness of malnutrition in technically underdeveloped areas of the world; extreme degrees of deficiency exist today in both human and animal populations due to grossly inadequate intakes of protein and other specific nutrients. (5) Experimental studies demonstrate genetic characteristics to be more important than nutritional factors. Comment: This is based on erroneous generalizations from work on inbred laboratory strains of animals having fairly uniform resistance and exposed to controlled infection. It does not usually apply to natural populations of diverse genetic background exposed to multiple infections. (6) Improving the diet or prescribing vitamins is ineffective in improving resistance to infection. Comment: This applies to diets already adequate and is irrelevant to understanding of the consequences of a deficient diet.

Working Generalizations. The following generalizations are proposed as a guide to continuing investigations in clinical and community medicine: (1) In human populations interaction between nutrition and infection is probably more important than the results of laboratory investigation would indicate. Greater response to nutritional influences occurs in host and agent populations of heterogenous genetic origin than in homogenous populations. (2) Synergism is the dominant interaction. No competent observer can witness the deaths from seemingly trivial infections of malnourished persons in technically underdeveloped areas or scan the list of causes of death

in such regions without realizing that large numbers of people are dying from infections ordinarily not fatal. Multiple infections with parasites and bacteria, larger infecting doses because of poor sanitation, genetic susceptibility, and environmental conditions are explanations commonly advanced for this high fatality. Wartime experiences and clinical evidence from wards of hospitals receiving large numbers of poorly nourished patients support many laboratory studies that synergism is of particular importance. Worldwide research on kwashiorkor demonstrates that protein deficient children are at high risk of fatal infection and with refeeding this risk steadily decreases. (3) That type of synergism in which infections contribute to malnutrition needs far more emphasis than it has received. With malnutrition so frequent in many parts of the world, infection often sets off a train of events resulting in death from malnutrition or a related terminal infection. Children might well survive one or the other but not both. (4) Adding nutrients to an already adequate diet usually has no effect on infections. The major exceptions are infections with certain intestinal parasites where secondary action on bacterial flora and other factors come into play, and less pertinently the highly questionable evidence on vitamin C. (5) The demonstrated antagonism between nutritional deficiencies and viral and protozoal infections has no recognized practical usefulness. (6) A gradient is evident, from a state of synergism characteristic of more or less free-living extracellular microorganisms, to antagonism with intracellular agents. While synergism occurs across the gradient, antagonistic phenomena appear only where organisms have obligate dependence on the enzyme systems of host cells. Based on type of microorganism the following patterns of interaction have been defined: a) Bacteria, rickettsiae and helminths are regularly synergistic with nutritional deficiencies; b) protozoa are as often antagonistic as synergistic; c) viruses are more often antagonistic than synergistic. (7) Patterns of interaction according to deficiencies in nutrients have the following characteristics: a) General inanition is regularly synergistic with most infections, but antagonism has been found with viruses and protozoa; b) protein deficiencies produce synergistic effects; rare instances of antagonism result from need of an infectious agent for a specific amino-acid; c) vitamin A deficiency is regularly synergistic; d) vitamin D deficiency commonly fails to interact with infections, but synergism has been demonstrated; e) vitamin B deficiencies result in synergism or antagonism depending upon agent and host; they are responsible for most known instances of antagonism; f) vitamin C deficiencies are usually synergistic, but antagonism has been demonstrated; g) specific minerals are either synergistic or antagonistic.

A Concluding Thought. A basic biologic fact has inadequate recognition. The interaction between nutrition and infection is dynamic, frequently characterized by synergism and less commonly by antagonism. The mistaken impression that this interrelation is of secondary importance does little harm in countries where malnutrition is rare. Where both malnutrition and infection are serious, as they are in most tropical and technically underdeveloped countries, success in control of either condition commonly depends on the other. Problems of nutrition and infectious disease are interdependent in laboratory experiments, in clinical management of patients and in public health programs.

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PHYSIOLOGY

PROCEEDINGS OF

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SEMINAR ON THE PHYSIOLOGY OF FEEDING BEHAVIOR

Feeding Behavior in the Insect. VINCENT G. DETHIER, PH.D. (Zoological Laboratory, University of Pennsylvania). Although insect behavior has a certain plasticity learning seems to play less of a role in day to day activities than innate (that is, genetically fixed) behavior patterns. The insect appears to be more rigorously stimulus-bound than animals higher in the phylogenetic scale. This dependency upon sensory stimuli is most readily seen in the feeding behavior of the blowfly where choice of food, rate of intake, and volume of intake are tightly controlled by input from the chemoreceptors of the legs, mouthparts, and antennae.

Each chemoreceptive organ of the blowfly which is concerned with taste is a long hollow hair innervated by two bipolar neurons whose cell bodies lie at the base of the hair and whose axons proceed, apparently without synapsing, to the central nervous system. Stimulation of one cell with carbohydrates of specific configuration initiates and drives feeding; stimulation of the other cell with such compounds as salts and acids prevents feeding. Stimulation of a single cell is sufficient to elicit a complete behavioral response.

Feeding has been studied by (1) measuring rate and volume of intake following stimulation of chemoreceptors; (2) measuring duration of feeding as a function of peripheral adaptation; (3) presenting flies with a choice of solutions in standard preference/aversion tests; (4) loading the mid- and hindgut; (5) ligating various areas of the gut; (6) altering blood-sugar levels; and (7) measuring food intake following section of the stomatogastric nervous system.

Data from these experiments show that feeding is initiated and driven by peripheral sensory input and terminated by negative feedback from the stomatogastric nervous system. The stimulating effectiveness of a food rather than its nutritional value is the crucial factor regulating feeding behavior.

Feeding Behavior in the Rodent. ELIOT STELLAR, PH.D. (Institute of Neurological Sciences, University of Pennsylvania School of Medicine). The basic principle in the present approach to feeding behavior in the rodent holds that feeding is under multifactor control, and therefore, is determined jointly by (1) sensory stimuli, (2) the internal environment, (3) central neural mechanisms, and (4) learning or habit. The relative contribution of these factors change in phylogeny so that sensory stimuli are of much greater importance in inframammalian organisms like the insect and learning or habit are of greater importance in man.

Study of the role of sensory stimuli in the rat is made by feeding a single food in solution such as glucose or sodium chloride. As concentration increases, ingestion increases up to the

point where negative taste factors or inhibitory post-ingestion factors, or both, enter; then ingestion progressively decreases. Controls involve loading solutions intragastrically and testing rats with esophageal fistulas.

Internal environment factors are studied by reducing salt levels through adrenalectomy and demonstrating changes in the ingestion of salt solutions with and without the administration of salt supplements.

The central neural mechanism is investigated by lesions and stimulation of the hypothalamus. Lesions near the ventromedial nucleus produce overeating and stimulation of this region inhibits feeding; conversely, lesions in the lateral hypothalamus cause starvation whereas stimulation of this area elicits feeding. Animals with ventromedial lesions are finicky in the sense that they overeat in response to certain stimuli and refuse to eat in response to others. Animals with lateral lesions may recover from starvation and during the course of recovery, they are responsive to certain food-stimuli and not at all to others.

The role of habit in feeding is shown in data from the literature where, for example, the adrenalectomized rat that has developed a preoperative preference for glucose fails to select salt in a choice of salt and glucose solutions and dies.

Feeding Behavior in Man. ALBERT STUNKARD, M.D. (Departments of Psychiatry and Medicine, University of Pennsylvania School of Medicine). A psychiatrist is moved to admiration at the completeness with which the systems regulating food intake can be described for the insect and the rodent. Such work stands as a paradigm in the effort to introduce the theoretical model of physiological regulations into the study of human behavior. Because of the great complexity of human behavior such an effort at the present time is perhaps best limited to attempts to describe short behavioral sequences. One such sequence is eating behavior. Study of the eating behavior of obese persons has revealed three deviant eating patterns:

1) The "night-eating syndrome" is characterized by morning anorexia, evening hyperphagia and insomnia. It occurs during periods of life stress and is apparently alleviated with relief of the stress. There is no consistent personal meaning of either the morning anorexia or the evening hyperphagia. Persons manifesting this syndrome usually express little self-condemnation related to their overeating.

2) The "eating binge" is characterized by the consumption of very large amounts of food within short periods of time, usually no more than a few hours. As with the night-eating syndrome, binge-eating seems to occur during periods of life stress. In contrast to the night-eating syndrome, however, binge-eating occurs with no periodicity and often seems to have personal (unconscious) meaning to the subject. It is regularly followed by severe discomfort and marked self-condemnation.

3) "Eating-without-satiation" is characterized by difficulty in stopping eating without any noticeable increase in the intensity of the desire for food. There is no apparent relation to periods of stress and a random occurrence throughout the day. Such eating has no apparent personal meaning to the subject and there is no associated self-condemnation. Alone among these patterns it seems to be associated with brain damage.

These deviant eating patterns occur in no more than 15% of obese persons and they augur ill for the success of attempts at weight reduction.

BOOK REVIEWS AND NOTICES

LEHRBUCH DER INNEREN MEDIZIN, VOL. 1 AND 2. Edited by HELMUT DENNIG. 4th ed. Pp. 920 and 892; 351 and 247 ills. respectively. Stuttgart: Georg Thieme Verlag, 1957 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $12.50.

IN the traditional German usage this textbook of medicine is published in two volumes. This is a most commendable feature: greater space permits better coverage (highly desirable in this day of ever expanding knowledge); it is more convenient to handle a lighter volume during prolonged reading (some one-volume English texts weigh nearly ten pounds); it permits a better grade of paper which, in turn, makes for better illustrations (these compare favorably with those of current English texts). Another aspect worthy of comment is the number of contributing authors: 12 as compared to 80 to 150 in our texts. It is clear that multiple authorship is necessitated by the complexity of professional knowledge and specialization. However, this reviewer suspects that reasons other than the excellence of text also enter into the picture. A point is reached when multiplicity of authors results in duplications and, paradoxically, in omissions. The reviewer does not suggest any optimal number of authors but he is impressed by the smoothness as well as the balance of this text presentation. In addition to the topics usually covered in textbooks of Internal Medicine, there is a good general chapter on diagnosis and treatment that makes reference, among other things, to massage, gymnastics, baths and spas, and psychotherapy. The chapter on poisons and poisonings is the best this reviewer has seen in a textbook. This, the 4th edition, in comparatively few years bespeaks the excellence of this work: it would be worthy of translation. R.K.

PATHOLOGY FOR THE PHYSICIAN. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), Emeritus Professor of Pathology, University of Toronto. 6th ed. Pp. 900; 489 ills. and 12 color plates. Philadelphia: Lea & Febiger, 1958. Price, $17.50.

THIS is, in many respects, a new book rather than a new edition. Large portions have been re-written, especially the sections on General Considerations at the opening of each chapter, involving as they do so much of the newer physiological, biochemical and cytological aspects of the subject. A new feature is the Table of Contents which heads each chapter and greatly facilitates a working acquaintance with the book for convenient reference. It is noteworthy that the author has avowedly done his re-writing with the graduate rather than the undergraduate student in mind, the physician or internist rather than the pathologist, the young rather than the old. The numerous illustrations continue to be of a high order of excellence. The book is warmly recommended. R.K.

LES HYPERCORTICISMES SURRÉNALIENS. By ETIENNE-EMILE BAULIEU, Faculte de Medecine, Paris. Pp. 142; 25 ills. Paris: Masson et Cie, 1958. Price, 1.400 fr.

THIS monograph is divided into two sections. The first is a general section dealing with the biosynthesis of adrenocortical hormones, the role of ACTH, the catabolism of the corticosteroids, and the physjologic action of the cortical hormones and their metabolites. This is followed by a chapter on assay of adrenocortical hormones, and on tests with stimulation by ACTH, and with suppression by cortisone, cortisol and related compounds. In the second section the individual syndromes and disease entities are presented: Cushing's syndrome, the virilizing syndromes, and hyperaldosteronism. In a brief last chapter of the second section the questions of "mixed syndromes," of a possible hypercorticism in acromegaly, and of adrenocortical hyperfunction in obesity are discussed critically. Throughout the book, emphasis is put on physiologic interpretation of clinical findings; the presentation is precise and lucid and thoroughly up-to-date. The bibliography contains 61 key references, arranged by chapters; numerous additional references to special problems are given in footnotes in the text; the author emphasizes in the introduction that he has not compiled a "general review" in the sense of a complete bibliography documenting every statement.

I should wish that my students would read this book; it is regrettable that my recommendation will have at best but a limited effect because so few medical stu-

dents read foreign languages. Should we not require reading knowledge in foreign languages for the M.D. degree, such as is already required for the degree of Ph.D.?

K.P.

ALLERGY IN PEDIATRIC PRACTICE. By WILLIAM B. SHERMAN, M.D., Associate Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, and WALTER R. KESSLER, M.D., PH.D., Instructor in Pediatrics, Columbia University College of Physicians and Surgeons. Pp. 296; 12 ills. and 2 color plates. St. Louis: C. V. Mosby Co., 1957. Price, $9.25.

SINCE most infants and children with allergic diseases are treated by general practitioners and physicians without special training in allergy, this book is intended by the authors to offer to such physicians practical aid in the diagnosis and treatment of these conditions. This objective they achieve exceedingly well. There is an adequate presentation of underlying theory to give a proper background. The clinical material is more than ample, with particular stress on the commoner conditions and on practical methods and procedures. Beyond the announced purpose are such things as the detailed list of allergens and dilutions for intracutaneous testing and the preparation of therapeutic house dust extracts. The presentation is uniformly good, simple and accurate. Noteworthy is the chapter on General Pediatric Care of the Allergic Child. The few illustrations are both good and well selected. The book should prove a welcome addition to the practitioner's library.

R.K.

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80 PUERTO RICAN FAMILIES IN NEW YORK CITY. HEALTH AND DISEASE STUDIED IN CONTEXT. By BEATRICE BISHOP BERLE, M.D. Pp. 331; 10 ills. New York: Columbia University Press, 1958. Price, $4.75.

THIS is a fascinating recital of the findings of an important study of health and disease in context. It is highly instructive: probably most instructive to the young physicians who had the opportunity under Doctor Berle's guidance and in the company of her associated social anthropologists to observe these Puerto Ricans in their home settings. This reviewer began his medical career as a general practitioner in an industrial area of a large city. He never lost the viewpoint and perspective which that experience provided. Over the years he has noted the increasing lack of such experience, viewpoint and perspective in teachers of medicine, especially the younger ones, who never left the ivory towers of their teaching hospitals. The attempt to recapture that viewpoint by programs of so-called "integrated" or "comprehensive" medicine will do much for those patients who come to hospital clinics; it will do even more for the medical students, who today have largely to learn these lessons by experience in their later practice; it will do most for the teachers themselves and for their concepts of the origin of symptoms in relation to the patient's total environment. But the medical hope of the general public, the overwhelming majority of whom are not treated by teachers or in teaching hospitals, lies in the up-grading of the trend of medical practice to which they have access, by the increasing application of group practice: tailored, modified and equipped to meet local needs. That in essence is what Doctor Berle and her associates did in the New York slum. This valuable book should be read by all teachers of medicine and by all young physicians and medical students.

R.K.

ABORTION IN THE UNITED STATES. Edited by MARY STEICHEN CALDERONE, M.D. Medical Director, Planned Parenthood Federation of America, Inc. Pp. 224. New York: Paul B. Hoeber, Inc., 1958. Price, $5.50.

THE material in this book consists of several introductory papers concerning various aspects of induced abortion and the general discussions stimulated by these presentations. The participants in this conference, which was sponsored by the Planned Parenthood Federation of America, were authoritative gynecologists, psychiatrists, sociologists, health officers and students of population. The general subjects included the legal aspects of abortion in this and other countries, illegal abortion, psychiatric and sociologic aspects of abortion and illegal abortion as a substitute for contraception.

Although a considerable volume of information concerning the causes and results of illegal induced abortion is available it certainly is incomplete and much of it is inaccurate and the deliberations of this conference serve to emphasize this fact. The participants are quite aware of this inadequacy and have recommended that an effort be made to explore the ". . . background, motivations, mechanisms and results. . . ." in women seeking abortion. They suggest that this information could be obtained in consultation

centers to which women could be referred for evaluation of the entire problem, not specifically for termination of pregnancy.

There is an excellent bibliography and four appendices. In the latter abortion and birth control laws for each of the states and for England are outlined and abortion in other countries is discussed.

While this book certainly is not the final answer to the problem of induced abortion it contains much interesting and valuable information and should prove helpful to physicians, social workers, lawyers, teachers and others who must deal with women who are seeking termination of pregnancy. J.W.

BRONCHOPULMONARY DISEASES: BASIC ASPECTS, DIAGNOSIS AND TREATMENT. Edited by EMIL A. NACLERIO, M.D., Chief of Thoracic Surgical Services. Harlem and Columbus Hospital, New York. Pp. 956; 719 ills. New York: Paul B. Hoeber, Inc., 1957. Price, $24.00.

THIS is an imposing and highly informative volume on all aspects of bronchopulmonary diseases. There are 115 chapters under 31 group headings, that cover, one might even say blanket, the subject. They have been written by no less than 142 authors, all of them selected for their outstanding competency in their respective fields. The book consequently has a high value as a reference work not only for general practitioners but for a wide range of medical and surgical specialists. When used as a reference work, there is no significant detriment in the fact that the book shows a certain amount of duplication of coverage as a result of such multiple authorship. The book should find a wide appeal. R.K.

L'AUTO-INTOXICATION APRÈS BRÛLURE. By T. GODFRAIND. Pp. 191; 49 ills. Brussels; A. Christiaens, s.a., 1958.

THE main purpose of the experiments here described was to test the validity of the hypothesis that a toxic substance or substances are released in the burned area. The first part of the study was the testing in frogs of the toxicity of various heated proteins and their split products. The evidence at hand suggests that the proteins become toxic only after proteolysis. In the second part of the study, carried out in rabbits, extended observations were made on the effects of various types of split products. The proteins of the edema fluid were separated by dialysis into two fractions: an insoluble one of euglobulins and a soluble fraction of albumins, cytoglobulins and some euglobulins. The euglobulin derivatives were far more toxic than the soluble fractions. This is an important contribution to the understanding of the pathology of burns. R.K.

CHOLESTEROL: CHEMISTRY, BIOCHEMISTRY AND PATHOLOGY. Edited by ROBERT P. COOK, University of St. Andrews, Queen's College, Dundee, Scotland. Pp. 542; 78 ills. New York: Academic Press Inc., 1958. Price, $15.00.

DURING recent years a tremendous, almost staggeringly large, literature has accumulated concerning cholesterol. Reasonably accurate methods of quantitative analysis have become available and there is a wealth of data on its concentration in the body fluids and tissues of man and other mammals under physiological and pathological conditions. Tracer techniques have permitted a selection among the numerous pathways of synthesis, and there have been derived more or less well-established concepts of its production in the animal organism from acetic acid and from certain branched C_5 and C_6 compounds which contain the isopentane or isoprene skeleton. Nevertheless nothing is actually known of its purpose in the metabolic economy. Numerous clues, however, have led to its implication as a pathogen *sui generis*, and the question that has been asked by Harry Deuel: "Cholesterol —Friend of Foe?" is indeed apropos. The present volume is an attempt to bring together all the important information (through 1957) concerning this fascinating compound. The monumental task has been extremely well done, and represents the efforts of 15 illustrious workers in this field. The chapter list includes: Historical Introduction, Chemistry, Methods of Isolation and Estimation, Distribution of Sterols, Physiology, Biosynthesis, Metabolism, Conversion to Steroid Hormones, Microscopical Localization in Cells and Tissues, Pathological Manifestations of Abnormal Metabolism, Treatment of Disorders of Cholesterol Metabolism, Evolutionary Aspects of Sterols, Requirements of Insects and Protozoa, Microbial Metabolism, Relations to Other Lipids, and an Appendix of Practical Methods. An extensive and excellent bibliography is very necessarily included. Biochemists, physiologists, pathologists and physicians interested in basic mechanisms in health and disease will find this volume stimulating reading and will want to have it handy for reference. It is highly recommended. T.D.

PSYCHOPHARMACOLOGY. PHARMACOLOGIC EFFECTS ON BEHAVIOR. PROGRESS IN NEUROBIOLOGY, III. Edited by HARRY H. PENNES, M.D., Consultant in Psychiatric Research, Department of Mental Hygiene, New York Psychiatric Institute. Pp. 362; 36 ills. New York: Paul B. Hoeber, Inc., 1958. Price, $8.00.

THIS volume is the third of a series on "Progress in Neurobiology," a series indicative of the current interest in this important field. It is a symposium in which 41 participants from many disciplines present results of their own investigations, and survey the existing literature in the field of psychopharmacology. Emphasis is placed on the biochemistry and experimental neuropharmacology of the major psychotomimetic and psychotherapeutic drugs. The problem of methodology in this difficult area is also considered, and the reader is reminded to exercise due caution in evaluating published reports, particularly with respect to clinical evaluations of "tranquilizing" drugs. In general, the book does not reduce the confusion prevalent in the field of psychopharmacology; it does emphasize the present state of empiricism. Researchers in this field will appreciate the stimulating discussions and the bibliographies. R.S.

ANNUAL EPIDEMIOLOGICAL AND VITAL STATISTICS, 1954. Pp. 617. Geneva: World Health Organization, 1957. Price, $10.00.

THIS is the seventh yearbook of epidemiological and vital statistics published by the World Health Organization. Part I gives brief data on areas and populations of the various countries and territories and statistics on causes of death. Part II gives the data for cases of, and deaths from, notifiable communicable and parasitic diseases and Part III (formerly published separately) presents statistics of Health Personnel, Hospital Establishments and Vaccinations throughout the World. All captions are printed in French and in English. The volume is a rich storehouse of scientific data of world wide nature and import and a significant testimonial to the growing strength and value of the world health movement under the sponsorship of the United Nations. R.K.

THE PSYCHOLOGY OF MEDICAL PRACTICE. By MARC H. HOLLENDER, M.D., Professor and Chairman, Department of Psychiatry, State University of New York. Pp. 276. Philadelphia and London: W. B. Saunders Company, 1958. Price, $6.50.

THE psychology of medical practice refers to the act of medicine. This book concentrates on the problems encountered in the everyday practice of medicine and what can be done about them. Four specialties: medicine, surgery, obstetrics and pediatrics, to which most time is usually allotted in the medical school curriculum have been singled out for special consideration.

This book is written in a clear, concise style and makes interesting reading. Two chapters on the doctor-patient relationship are unusually valuable. A chapter concerning "The Patient with Carcinoma" will be welcomed by the physician. Dr. Leonard A. Stine, Ernest M. Solomon and Julius B. Richmond are contributors to the book. M.B.

DANGEROUS PROPERTIES OF INDUSTRIAL MATERIALS. By N. IRVING SAX, Consultant on Industrial Safety, Nuclear Development Corporation of America, White Plains, New York. Assisted by LEONARD J. GOLDWATER, WILLIAM B. HARRIS, JOHN H. HARLEY, JOSEPH J. FITZGERALD, AND MILTON S. DUNN. Pp. 1467; illustrated. New York: Reinhold Publishing Corporation, 1957. Price, $19.50.

THIS is a completely revised and enlarged edition of the Handbook of Dangerous Materials. It has the broad purpose of presenting the manifold hazards which accompany the use of materials in industry, to explain the area in which such hazards present themselves and how to meet them to insure safety in day-to-day operation. The book begins with nine sections whose titles are significant; Toxicology, Ventilation Control, Personnel Protection and Personal Hygiene, Atmospheric Pollution, Radiation Hazards, Industrial Fire Protection, Storage and Handling of Hazardous Materials, Reactor Safeguards, and Allergic Disease in Industry. Section 10, whose 1057 pages constitute the bulk of the volume, lists nearly nine thousand substances and under each one gives a brief description of the substance, the hazards which present, and references to the pertinent earlier sections which tell how those hazards are to be met. Section 11 gives Shipping Regulations and Section 12 is an Index to Synonyms. This volume should, of course, prove indispensible to the industrial physician and industrial hygienist and safety man and to the thousands who ship, receive or transport possibly danger-

cus materials. It should also be available to physicians in emergency wards and dispensaries and it should be in the possession of those who practice in highly industrial communities. R.K.

MEDICAL ELECTRICAL EQUIPMENT: PRINCIPLES, INSTALLATION, OPERATION, MAINTENANCE. Edited by ROBERT E. MOLLOY, M.B., F.F.A., R.C.S. Pp. 312; 238 ills. New York: Philosophical Library, Inc., 1958. Price, $15.00.

THIS volume, to which contributions have been made by numerous authors, has been edited by Robert E. Molloy. It represents an attempt to discuss the various types of electrical equipment used by the medical profession. Included are sections on lighting, air conditioning, diathermy, Roentgen-ray, special diagnostic instruments, and other types of electrical equipment such as sterilizers and paging systems.

The book is written in a very concise fashion and is directed toward the physician or the administrator who does not have a complete knowledge of electricity. It should prove to be a valuable reference volume for anyone having the responsibility of using or purchasing electrical equipment for office or hospital use. R.B.

Therapeutic Uses of Adhesive Tape. 2nd ed. Pp. 130; 99 ills., 7 in color. New Brunswick, New Jersey: Johnson & Johnson Company, 1958. Free to physicians and athletic directors on request.

THIS is the second edition of a manual, which has been published by the Johnson & Johnson Company, covering the therapeutic uses of adhesive tape. The first section is devoted to the general principles of using tape; there is an excellent section on sensitivity reactions. The remaining chapters cover the various ways in which adhesive tape can be used in treatment and in general bandaging. There is a good section on athletic injuries. The illustrations are numerous and support the text well.

This book is recommended as a manual to which one may refer for various methods of adhesive tape bandaging and strapping.

R.B.

Food and You. BY EDMUND SIGURD NASSET, B.A., M.S., PH.D,. Professor of Physiology School of Medicine and Dentistry, University of Rochester. 2nd ed. Pp. 166; New York: Barnes and Noble, Inc., 1958. Price, $1.25.

THIS manual contains a concise, non-technical account of the importance of food, its composition, utilization and function in human physiology. The terminology employed avoids medical or scientific phrases; where used, they are defined in simple, yet adequate, language. The author has the faculty of presenting the story of nutrition in an attractive, informative style which should make this new edition interesting reading for the lay public. C.S.

Laboratory Instructions in Biochemistry. BY ISRAEL S. KLEINER, PH.D., Professor of Biochemistry, New York Medical College, and LOUIS B. DOTTI, PH.D., Chemist, St. Luke's Hospital, New York. 5th ed. Pp. 289; 9 ills. St. Louis: C. V. Mosby Co., 1958. Price, $3.50.

A NEW and revised edition of an excellent manual designed for use in connection with medical school biochemistry courses. It has been developed by many years of experience in instruction and is a very practical and usable laboratory text. It contains accessory tables such as logarithms, atomic weights, metric equivalents, normal values for blood, serum, urine, feces, and others.

It has a number of deficiences which may become apparent when it is used in laboratories equipped differently from the authors'. For example, photometric measurements and calculations of results in quantitative photometric analysis are discussed only in relation to the use of the Klett-Summerson photoelectric colorimeter. The theory of photometery is covered only very sketchily.

The authors' practice of not including the composition of the reagents used in a method (reagent preparation is given in an appendix), although it results in simplified presentation of the method, restricts the students' comprehension of the chemical reactions involved.

The text material is printed on only one side of the sheet, leaving the other side blank for student notes. The pages are sewn, and are covered with a good, water resistant paper cover, which is, however, insecurely glued on.

J.B.

Experimental Pharmacodynamics. BY T. KOPPANYI AND A. G. KARCZMAR. 2nd ed. Pp. 258; 32 ills. Minneapolis; Burgess Publishing Company, 1958. Price, $5.50.

THIS is a well known laboratory manual suitable for the laboratory instruction of medical, dental and pharmacy students in pharmacology.

R.S.

Therapeutique Neurologique et Psychiatrique. BY PAUL COSSA, Chief of Neurological Service of Nice Hospital. 2nd ed. Pp. 607. Paris: Masson et Cie, 1958. Price, 5.800 fr.

THIS is a comprehensive treatise on the treatment of neurological and psychiatric diseases, with the exception of brain and spinal cord tumors and brain abscess, treatment of which are regarded as the province of the neurosurgeon. Little can be said regarding the treatment of

specific diseases, since the medications in use are often not familiar to neurologists in this country. This usually proves to be of little consequence, since the discussion of treatment in each disease is introduced by a clear and concise rationale of the principles underlying the therapy. This is by all odds the most interesting and instructive feature of the volume, and for this alone it can be recommended to all those interested in treatment in neuropsychiatry.

B.A.

Pediatric Methods and Standards. Edited by FRED H. HARVIE, M. D., University of Pennsylvania. 3rd ed. Pp. 324. Philadelphia: Lea & Febiger, 1958. Price, $4.00.

THE third edition of this pocket-sized book is as admirable as its predecessors. It well covers the problems met in general pediatric practice in a precise and up-to-date manner. Pediatricians and general practitioners treating children should have this book constantly available. R.G.

Handbook of Cardiology for Nurses. BY WALTER MODELL, M.D., Associate Professor of Medicine, Cornell University Medical College, and DORIS R. SCHWARTZ, R.N., Assistant Professor, Cornell University New York Hospital School of Nursing. 3rd ed. Pp. 328. New York: Springer Publishing Co., 1958. Price, $4.50.

A THIRD edition in 6 years is eloquent testimony to the popularity of this book. It is written specifically for nurses and allows for organized instruction in cardiology. The nurse's role in the care of the person with heart disease is emphasized. Study of this book should result in a knowledgeable, efficient and sympathetic nurse who will contribute much in the restoration of a cardiac to a normal useful life. J.Z.

Comparative Clinical and Biological Effects of Alkylating Agents. BY LEON H. SCHMIDT AND 108 OTHERS. Pp. 610; illustrated. New York: New York Academy of Sciences, 1958.

THIS volume consists of a series of papers presented at a conference held under the auspices of the New York Academy of Sciences and the Cancer Chemotherapy National Service Center, Bethesda, in March, 1957. The chemistry and biological effect of alkylating agents and the results of their clinical use in the treatment of cancer are considered in turn.

Workers in cancer chemotherapy will find this collection to contain much interesting and worthwhile information. C. Z.

Standard Methods of Clinical Chemistry. Vol. II. Edited by DAVID SELIGSON. Pp. 217; illustrated. New York: Academic Press, Inc., 1958. Price, $5.50.

THIS is the second in a series of volumes in which it is planned to publish standard chemical methods for use in clinical laboratories under the sponsorship of the American Association of Clinical Chemists. As with the first volume, accuracy is the basis for selection of a method. The procedures described include tests for calcium, chloride, serum cholesterol, serum iron, protein bound iodine, nonprotein nitrogen, blood pH, alkaline and acid phosphatase, plasma phosphatides, urobilinogen, urinary porphyrins, hemoglobin, and total fatty acids in stool. Several alternative methods are given for tests which were given in Volume I.

All laboratories responsible for clinical chemical determinations will wish to have this book for reference. C. Z.

Bioenergetics. BY ALBERT SZENT-GYÖRGYI, Institute for Muscle Research of the Marine Laboratory, Woods Hole, Mass. Pp. 143; 28 ills., 1 in color. New York: Academic Press, Inc., 1957. Price, $4.50.

THE problem of how energy moves myosin is considered in this book. The stature of the author is well established. He presents a theory of energy transmission. Absorption, fluorescence and phosphorescence are considered. Chapters are included on his theory of muscular contraction, ATP, Riboflavine, on ions, glutathione, sugars and alcohols, and on oxidative phosphorylation and its uncoupling and depolarization of the cell membrane. The final section deals with drugs, hormones and disease. Iodine and chlorpromazine represent drugs. The disease presented is myotonia and the hormone is the thymus.

M. O.

Makrobiotik oder Die Kunst das menschliche Leben zu Verlängern. BY CHRISTOPH WILHELM HUFELAND; PROF. DR. F. LEJEUNE, ed.; 8th ed., 1860. (reprint with foreword and annotations). Pp. 294; 1 ills. Stuttgart: Hippokrates-Verlag, 1958. Price, DM 14.80.

THE publishers of this volume are to be congratulated for reprinting a revised version of a famous book by a great physician published first in 1796. What this pioneer of prophylaxis had to say is very much worth reading today not only by historians but also by students of public health and of education. W. E.

Oh, Baby! For Parents—Would Be, Could Be, and Have Been. "Cartoons" BY MIKE ANGELO. Pp. 64. Philadelphia: The John C. Winston Company, 1958. Price, $2.50.

"OH, BABY" is a book of cartoons "for parents—would be, could be and have been." Many of the situations are quite familiar because the parents, for whom the book is intended, can either recognize them as familiar to their own experiences or have seen them depicted in cartoons before. Most of them, however, are quite amusing. The cartoons are repeated in

reduced size and on gummed paper so the purchaser can paste them on letters, packages, etc. This book might well be placed in a physician's waiting room or sent to young married couples or new parents. J. W.

Manipulativmassage im Rahmen de physikalischen Therapie. By Dr. Med. J. C. Terrier, Pp. 88; 49 ills. Stuttgart: Hippokrates-Verlag, 1958. Price, DM 12.80.

Fibroses Pulmonaires et Insuffisances Respiratoires Chroniques. By P. Laval. Pp. 294; 77 ills. Paris: Masson et Cie, 1958. Price, 3.500 fr.

Guide to Medical Writing. By Henry A. Davidson, M.D., Editor, Journal of the Medical Society of New Jersey. Pp. 338; 12 ills. New York: The Ronald Press Co., 1957. Price, $5.00.

This author knows how to write well and he knows how to tell about it to others. The book is, therefore, an excellent guide for every writer, and even the most experienced will find here many useful nuggets of information. Thanks to its clear and sprightly style, the book will be found entertaining as well as instructive.

R. K.

Genetic Resistance to Disease in Domestic Animals. By Frederick B. Hutt, New York State College of Agriculture, Cornell University. Pp. 198; 30 ills. Ithaca, New York: Cornell University Press, 1958. Price, $3.50.

The author presents his own views and cites the observations of others to the effect that the natural resistance of domestic animals to disease can be raised by selective breeding. Readers of this journal who are interested in the genetics of natural resistance will find in this little volume valuable information not easily accessible to students of human biology. E. S.

Half Life of Rhenium and Ages of Minerals. By Stanley N. Naldrett. Pp. 10; 2 ills. New York: New York Academy of Sciences, 1958.

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Dr. Richard A. Kern, Temple University School of Medicine, Philadelphia 40, Pa.

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